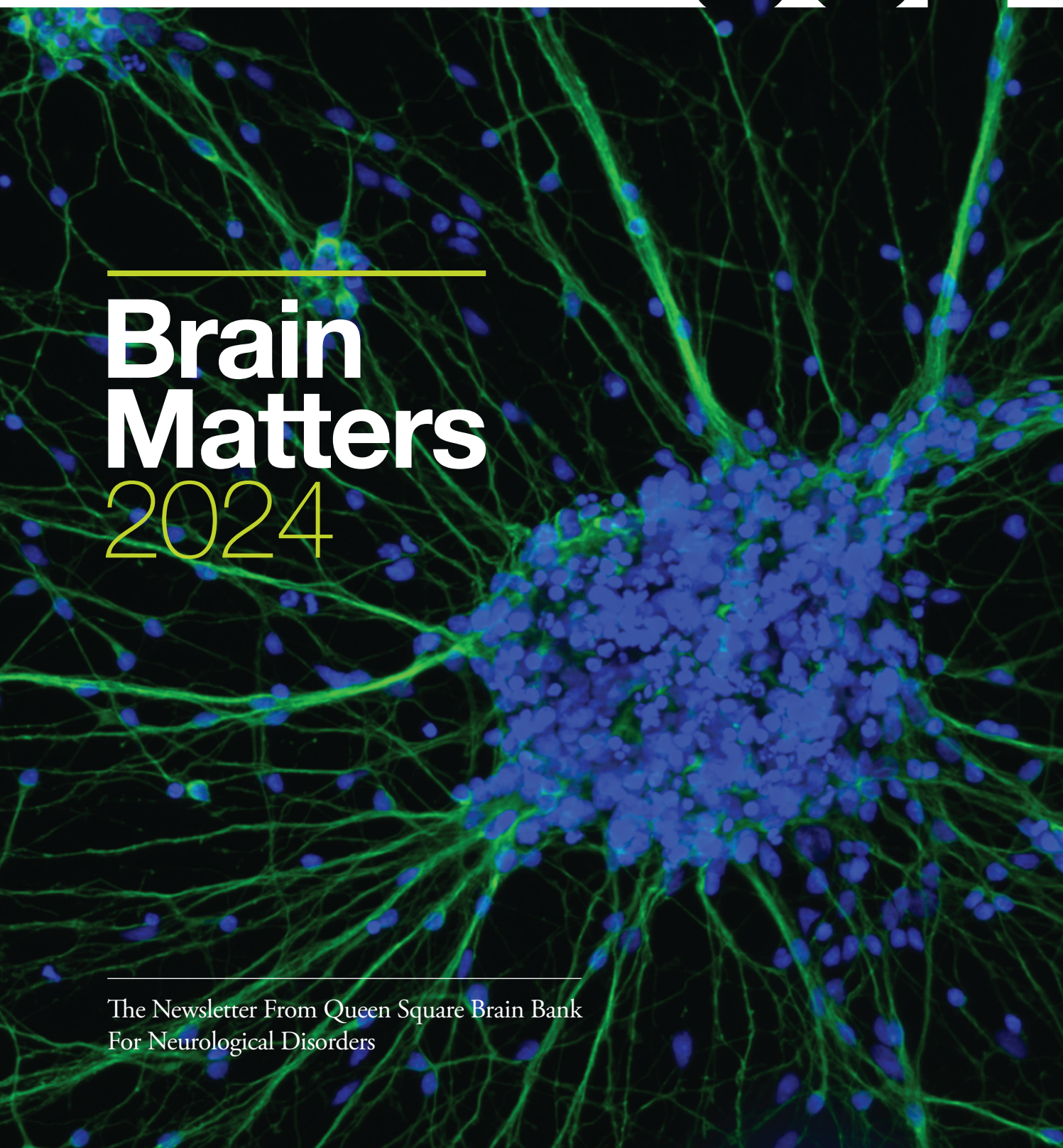
QUEEN SQUARE BRAIN BANK

UCL



Brain Matters 2024

The Newsletter From Queen Square Brain Bank
For Neurological Disorders

Professor Tom Warner, Head of Queen Square Brain Bank welcomes you to Brain Matters 2024:

The Queen Square Brain Bank (QSBB) has been fortunate to have dedicated and skilled staff who have worked selflessly for many years. The downside of this model is that there comes a time where sadly they have to leave or retire, and 2023 was such a year. We had to say goodbye and thank you to two key staff, **Kate Strand**, (brain bank manager) and **Karen Shaw**, (QSBB research nurse specialist). We are indebted to them both for their expertise and hard work for many years and wish them well for the future. We were lucky to have been able to appoint from within, and **Natalie Woodman** has taken on the manager role, and **Maggie Burrows** the QSBB research nurse position.

On the research side **Dr Patrick Cullinane** completed his research project on Parkinson's Disease and Progressive Supranuclear Palsy and has returned to Dublin to complete his clinical training as a neurologist, and his PhD thesis. Patrick is a talented clinician scientist and we are pleased that he will return in 2024, having been awarded an Edmond J Safra Fellowship at the Queen Square Movement Disorders Centre.

We are also delighted to welcome our new neuropathologist, **Associate Professor Karl Frontzek** who has joined us from Zurich. Karl will work at QSBB for half of his time, with the rest of his time spent as consultant neuropathologist at the Division of Neuropathology, National Hospital for Neurology and Neurosurgery. He will be contributing to the pathological diagnostic work at the brain bank as well as developing his own research.

In July 2023 the brain bank had an inspection by the Human Tissue Authority which is the body that oversees all UK human tissue biobanks and ensures that they comply with all legal and ethical governance. The QSBB was complemented on its processes and staff training, and only had minor areas to address, which is reassuring to us all.

Further good news for 2024. The QSBB has been awarded £1M from the Medical Research Council to expand the work we do by recruiting new clinical cohorts of patients with neurodegenerative conditions and develop access for researchers to study the tissue as well as the "in-life" investigations such as brain imaging, genetics and clinical data. It will also link us to other MRC funded brain banks and develop a "state of the art" database to allow researchers to search the best tissue for their projects. It is also recognition of the standing of the brain bank and its work.

As ever, none of the work we do would be possible without the generosity of the individuals who donate brain tissue to the QSBB and their families. We also thank donors who have contributed funding for our work.

2024

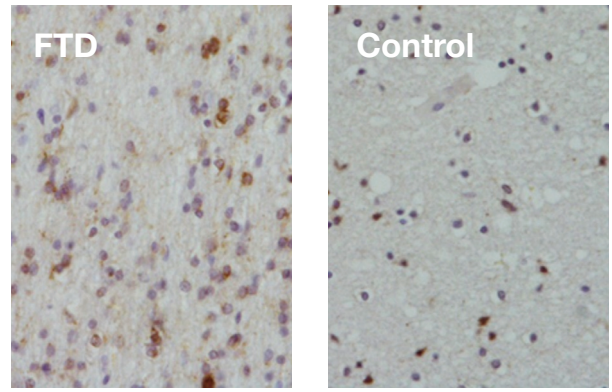
Research

Dr Conceição Bettencourt, Senior Research Fellow, and her team, Ms Kate Fodder, PhD Student and Ms Naiomi Rambarack, Research Assistant are investigating DNA methylation alterations in frontotemporal dementias:

Frontotemporal dementias (FTD) are neurodegenerative illnesses which cause problems with personality, behaviour, language and memory. The onset of FTD is usually before the age of 65, and currently there are no effective treatments.

Lumps of sticky proteins, such as those called TDP-43 and tau, form in brain cells of individuals with FTD, leading to cell dysfunction and eventually death. Cells depend on several things to function properly and survive. DNA provides the script, a sequence of letters, for different proteins to be made. This sequence is the same in all cells of the body, so cells require additional instructions to know how the script should effectively be read and what type of cell it becomes e.g. a blood cell or a nerve cell. A chemical modification to the DNA, called methylation, can give such additional instructions by working like a dimmer switch to control how much of each protein to make. Recent studies have shown that DNA methylation is important in some dementias, including Alzheimer's disease. However, DNA methylation has not been well studied in FTD.

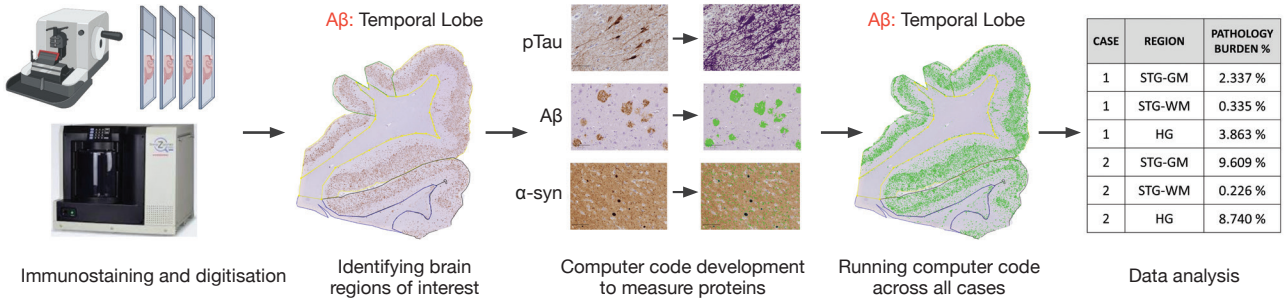
We compared DNA methylation in brain tissue from individuals with FTD and healthy people. We found significant differences in several genes and that these genes also had changes in the quantity of proteins they made, such as OTUD4. These changes may contribute to how brain cells die in frontotemporal dementias. The study involves Kate Fodder, a PhD student, and other members of the Bettencourt lab. We are looking for new molecules and abnormalities in certain brain cells that could reveal mechanisms underlying other brain disease and identify new potential treatments. Because DNA methylation can be reversed with appropriate drugs, finding out where abnormal methylation happens is important. If changes are detected early, they could help improve diagnosis and find biomarkers to track the disease and test treatments in future trials.



Images above: Microscopic view of brain tissue showing higher amounts of the protein OTUD4 (in brown) in the frontotemporal dementia brain (FTD), compared to a healthy brain (control).

Dr Zane Jaunmuktane and her team, Hemanth Nelvagal, Yau Mun Lin, Toby Curless and Nancy Chiraki are quantifying molecules and disease-causing protein aggregates with computer-trained codes.

Many diseases which lead to dementia and movement problems are caused by the progressive accumulation of protein clumps in the brain. With increasing age and other largely unknown factors, a range of different native proteins are prone to change their shapes and aggregate in neurones and glial cells. Diseases are distinguished by determining in which cell types and anatomical regions a particular protein has aggregated. This is done by detecting abnormal proteins by staining the tissue samples with antibodies and looking at the tissues under a microscope. In this project, funded by Aligning Science Across Parkinson's disease (ASAP), we are developing computer-trained codes to enable automated and consistent quantification of all common proteins prone to aggregation in the brains of people who had Parkinson's disease (PD). First we generated a digital slide collection, which means that these slides can be viewed at a high resolution on a computer. Next, we are training a computer programme to accurately identify the clumps and determine the burden of each abnormal protein in multiple brain regions across large



CASE	REGION	PATHOLOGY BURDEN %
1	STG-GM	2.337 %
1	STG-WM	0.335 %
1	HG	3.863 %
2	STG-GM	9.609 %
2	STG-WM	0.226 %
2	HG	8.740 %

Figure above: The pipeline for developing computer-trained codes for quantification of protein aggregates.

numbers of cases. This data will allow us to group different cases based on the extent of pathology. Notably, this type of analysis not only increases the diagnostic accuracy diagnosing neurodegenerative conditions such as PD but may help identify new patterns which may help develop more effective therapies.

In parallel to developing computer-trained codes for quantification of protein clumps, we are investigating intermediate molecules that link the genetic code and PD-associated alpha-synuclein protein. These intermediate molecules of RHA, called transcriptome, can inform on the workings of all cells. We are examining the intermediate products (transcripts) in a spatial context using a method called spatial transcriptomics, which allows us to determine transcripts in distinct brain areas and cell types.

Together with accurately quantified pathological protein burden and key clinical data, such as disease duration and genetic risk factors, spatial transcriptomics analysis will allow us to identify biological processes underpinning PD. This information will help development of biological markers which can be measured in patients to improve early diagnosis, and early treatment of patients.

Dr Nuria Seto-Salvia, Senior Postdoctoral Researcher, investigates the cellular and molecular mechanisms of DYT-TOR1A (DYT1) dystonia, which is a rare severe childhood-onset movement disorder, caused by an autosomal dominant mutation in the *TOR1A* gene.

People with dystonia develop involuntary muscle spasms and in DYT-TOR1A (DYT1) dystonia this typically leads to involvement of the arms, legs and back. Mutations in this gene have low penetrance, with approximately only 30% of those with the genetic change developing dystonia, and variable clinical features even in individuals of the same family. At present, there are some treatments available, but the condition cannot be cured, meaning many have life-long disability.

To develop new treatments we need to identify pathways in brain cells that lead to the disorganised control of movement. Animal models have helped to understand some of the biochemical, and cellular changes, including structural abnormalities at the membrane surrounding the nucleus and its connections with the endoplasmic reticulum, where proteins are made. However, these models cannot fully replicate all the features of dystonia in humans.

Dr Seto-Salvia is studying gene expression in human cell models of DYT-TOR1A dystonia using induced pluripotent stem cells (iPSC) from patients, derived from skins cells from people with and without dystonia. The stem cells can be grown in dishes and turned into neurons to allow study of their function. Analysis of the expression pattern of genes in these cells, as well as in cells from samples of brain tissue held at the QSBB, show a high number of up and down regulated genes in all neurons and brain tissue in dystonia patients. Further analysis between all cell lines and brain tissue identified 96 genes downregulated and 73 upregulated in dystonia, highlighting a number of potential pathways involved.

We are now looking at the key genes identified which are relevant to developing dystonia, and will study their function to identify possible therapeutic targets.

Q&A with Lynn Haddon, Brain Donation Co-ordinator.

I feel very lucky to work at the QSBB in a pivotal role supporting you, our potential donors, and by contributing to this year's newsletter, I have the chance to say thank you to all of you for supporting our research.

Many of you will have registered for our scheme since January 2015 when I started at the brain bank and will have 'met' me, others I will have spoken to over the years, some of our longstanding potential donors may have never 'met' me – 'Hello'.

What is your role at the QSBB?
I maintain our donor register and deal with questions our donors and their families have when first considering donation. Later when situations change, and new questions arise, I am at the end of the phone or email.

Equally important, I organise brain donations on behalf of our potential donor families. Each donation presents different circumstances, individuals, locations and timescales to manage. At a very difficult time for every family, my aim is to achieve the brain donation with minimal stress for the family.

Around 70% of my work involves interaction with you and the wider public, hospitals, funeral directors, care home staff, GPs... the list is long. I also have an administrative responsibility at the brain bank, ensure that our processes are fit for purpose, our working practices conform to Human Tissue Authority standards (by which we are governed) and that oversight and governance takes place and is recorded appropriately. I also support the QSBB team in our work to provide a final histopathology report for each donated brain which provides our families with a definitive diagnosis.

What would you say is your biggest challenge?
We miss out on very few donations but arranging them can be very difficult sometimes. My negotiation skills can be tested to the limit; no-one is obliged to help us. Mostly, my trust in human nature is rewarded and we are successful but on the rare occasions we are not, it can be very upsetting not only for the family but also for me and the brain bank team. Overcoming the challenges actually provides the reward. No day is ever the same, I love that.

In conclusion, I am proud to work at the Brain Bank and always humbled by the altruism of you, our potential donors. I look forward to talking to you whenever you need us. Thank you for your continuing support.

Contributors

From left to right:
Dr Conceição Bettencourt,
Kate Fodder, Naiomi Rambarack,
Dr Zane Jaunmuktane,
Hemanth Nelvagal, Yau Mun Lin,
Toby Curless, Nancy Chiraki,
Dr Nuria Seto-Salvia, Maggie Burrows.

Donations

Co-ordinators:
Lynn Haddon (pictured overleaf), Cheryl Pearce (above left), Natalie Woodman (above right).

Brain donation coordinators

QSBB Administrators, **Lynn Haddon** and **Cheryl Pearce** are often the first point of contact for potential donors. Coordinating the brain donor scheme with help from QSBB Lab Manager **Natalie Woodman**, the team work closely with relatives, hospital staff, funeral directors and couriers to ensure the careful donation and safe receipt of tissue, with the minimum of distress to families.

The importance of controls

We encourage people without a neurological condition, 'controls' to register with our donor scheme. Control tissue is vital for comparison with disease and provides researchers with an understanding of the normal appearance and function of the brain.

If you would like further information please log on to the website: **www.ucl.ac.uk/ion/qsbb**

Or contact Lynn Haddon **l.haddon@ucl.ac.uk** and Cheryl Pearce **cheryl.pearce@ucl.ac.uk**

Telephone: **020 7837 8370**

QS
BB

Brain banking

Brain banking is expensive and we continue to depend almost entirely on charitable benefactions for our survival. The QSBB is primarily funded by donations from the Reta Lila Weston Institute of Neurological Studies. We gratefully acknowledge the generosity of donor families, sponsors and several benefactors.

If you would like to offer a financial donation to help our research, please visit our website: www.ucl.ac.uk/ion/qsbb or contact Lynn Haddon.

Thank you.

Sponsors

UCL Queen Square Institute of Neurology

Reta Lila Weston Institute of Neurological Studies

Multiple System Atrophy Trust

Rosetrees Trust

Aligning Science Across Parkinsons's (ASAP)

Guarantors of Brain

Medical Research Council

Cover image shows: Cultured cortical neurons grown from induced pluripotent stem cells