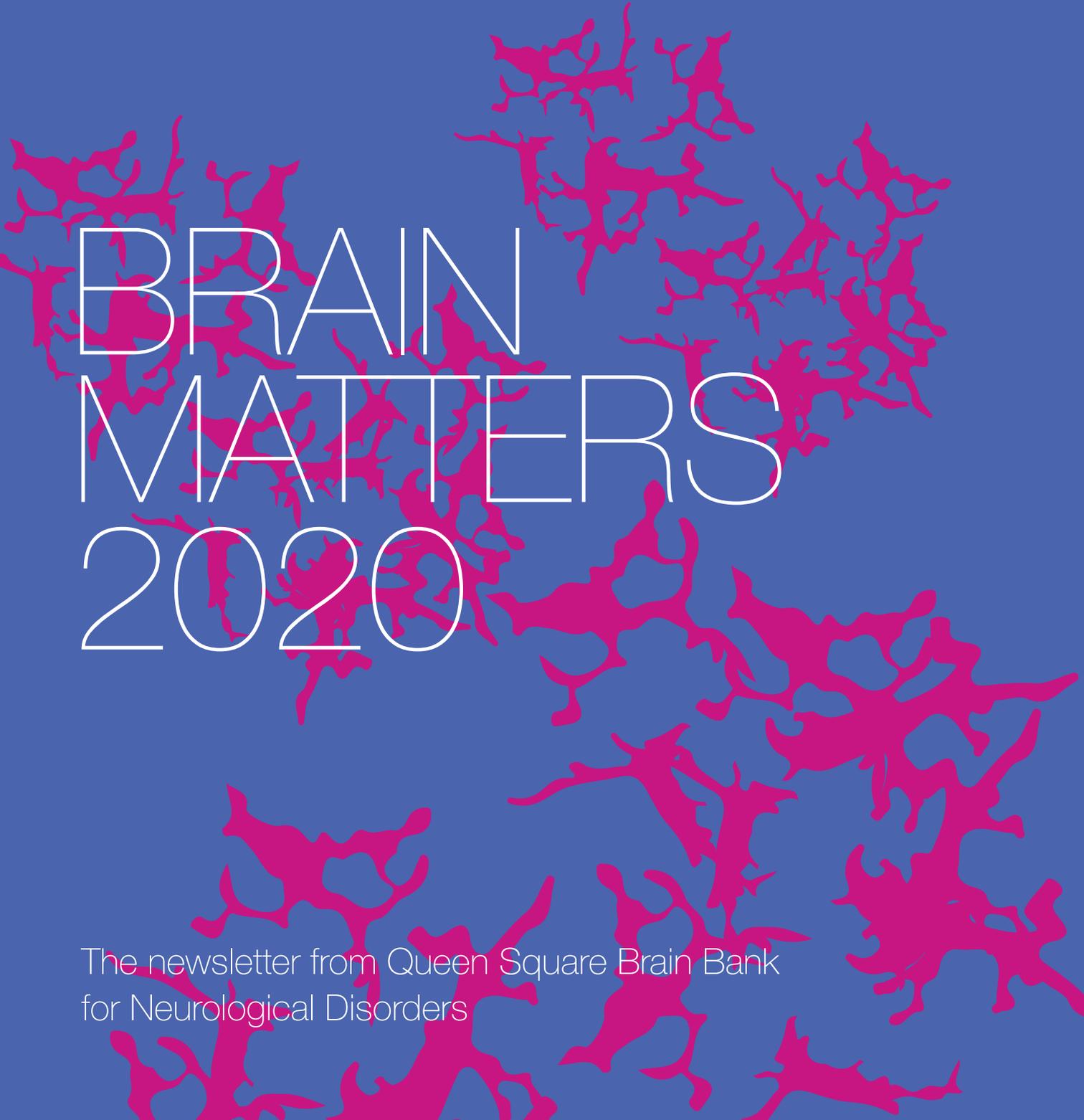


QUEEN SQUARE BRAIN BANK



UCL

A large, semi-transparent pink overlay of a brain scan, likely an MRI or PET scan, showing various brain structures and activity patterns. It is centered on the page and partially behind the main title.

BRAIN MATTERS 2020

The newsletter from Queen Square Brain Bank
for Neurological Disorders



Professor Tom Warner, Head of Queen Square Brain Bank welcomes you to the latest edition of Brain Matters.

2019 was another productive year for the team at Queen Square Brain Bank (QSBB), highlights of which are covered in the following articles.

One particularly memorable occasion was the 50th Anniversary Symposium of the Reta Lila Weston Institute of Neurological Studies, a key partner and funder of the brain bank. Attended by the Board of Trustees (right) and University College London Provost, Professor Michael Arthur, Dean of Faculty of Brain Sciences, Professor Alan Thompson and Director of UCL Queen Square Institute of Neurology, Professor Michael Hanna – the event showcased the accomplishments of QSBB.

A major factor behind our success is the team of long serving, committed staff who have spent many years dedicated to the curation and study of donated tissue. However, a down side of this remarkable continuity is that there comes a time when retirement beckons and 2019 was such a year for two members. In March Professor Janice Holton, Director of Neuropathology retired after eighteen years of service, during which she became an international neuropathology expert, diagnosing hundreds of cases of neurodegenerative disease and establishing a world class programme of research in Parkinson's disease and multiple system atrophy. We are delighted that despite leaving her full time role, Janice has become Emeritus Professor and will continue to pursue her interests on a part time basis.



Brain Bank Manager Linda Parsons is also leaving after thirty four years. During her tenure Linda has seen the brain bank grow from humble origins to a globally recognised research and tissue resource. Linda has shown continuous diligence and dedication over the decades, for which we are very grateful, and wish her a long and fulfilling retirement.

Restructuring the team is in progress to reflect these changes and to ensure we deliver a valuable service for future years. Dr Tammarny Lashley, Senior Research Fellow funded by Alzheimer's Research UK has been appointed Director of Research and will work to identify scientific opportunities to continue the schedule of high calibre research projects.

Most importantly, we remain indebted to the brain donors and their families whose altruism, generosity and support have underpinned the achievements of Queen Square Brain Bank in our mission to find the causes for and treatments of an array of neurodegenerative illnesses.

“A major factor behind our success is the team of long serving, committed staff who have spent many years dedicated to the curation and study of donated tissue.”

Research

Post-doctoral Clinical Research Fellow, Dr Eduardo Fernandez continues his studies to improve the quality of care for people with Parkinson's disease:

Parkinson's disease is typically recognised by tremor, stiffness, slowness of movement and walking difficulties. Severity of symptoms, response to medication and onset of complications such as falls and dementia can be highly variable. Neurologists have previously suggested categorising or grouping patients with similar features in order to predict illness progression and plan individualised care. Unfortunately, such systems are often too complex to use in clinical practice and have not incorporated recent advances in indicators of prognosis.

By reviewing the comprehensive medical records of 111 donors with post-mortem confirmed Parkinson's disease, the team at QSBB wanted to determine whether a simple clinical assessment undertaken at the time of diagnosis could accurately predict symptom development, disability and life expectancy. Donors were classified into three groups: mild, moderate and severe based on the extent of their movement impairment, memory and thinking difficulties, dream enactment and autonomic symptoms such as fall in blood pressure, constipation and urinary incontinence.

The findings confirmed that those placed in the severe group had experienced a more rapid deterioration, while people in the mild group had gradual symptom progression and had lived with the condition for longer. Our analysis of donors' brain tissue to determine differences in pattern or speed of damage that could explain this, revealed Parkinson's disease pathology was widespread in all the groups. However for those in the mild group, we suspect the brain damage had accumulated at a slower pace.

The results were published in a prestigious medical journal and concluded that Parkinson's disease is a single entity but with different rates of deterioration both clinically and pathologically, and that initial categorisation is helpful in predicting an individual's future illness and care needs.

Senior Research Fellow, Dr Rina Bandopadhyay is studying new ways to identify the early stages of Parkinson's disease:

Parkinson's disease is one of several neurodegenerative disorders that result from naturally occurring proteins folding into the wrong shape, fusing inappropriately with other proteins and eventually forming abnormal clumps in brain cells. The pathological hallmark as seen under a microscope is the Lewy body, which is made up of atypical forms of the protein alpha-synuclein.

There are several harmful changes that can happen to this protein before it actually forms Lewy bodies. Nerve cells detect and react to changes in the internal and external environment and one way they adjust is by an activity called chemical modification of proteins. Using tissue from QSBB, our findings show that these modifications occur at the start of the disease, increase over time and can be damaging to the cell. By studying the complex composition of alpha-synuclein and Lewy bodies we are expanding knowledge of these preliminary stages.

Previously, effective tools to do this were unavailable. Advances in new technology now enable us to understand more about the condition and analyse the associated chain of events. In order to help the patient there is a crucial need for early diagnosis and effective treatment that can halt the progression of the illness. Understanding the role of alpha-synuclein in normal physiology and in disease may aid this development.

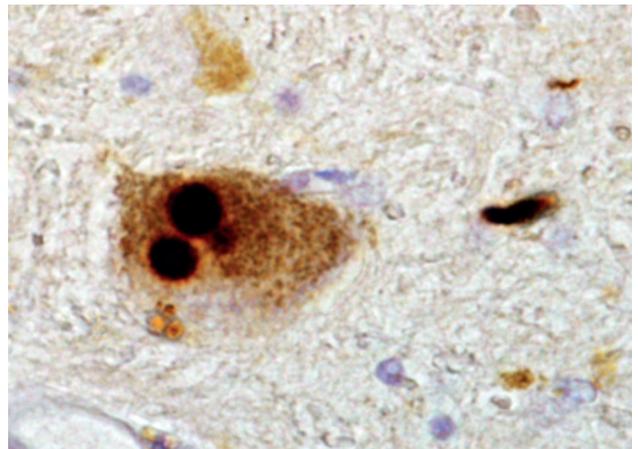


Image above: Microscopic view of two round Lewy bodies (dark brown in colour) within a nerve cell that contains modified alpha-synuclein.

Dr Christina Toomey, Research Associate and Dr Tammaryn Lashley, Director of Research are evaluating potential biomarkers for Alzheimer's disease:

Alzheimer's disease is the most common neurodegenerative illness and primarily affects a person's memory. Presently a clinical diagnosis can only be made after symptoms have begun and the pathology has already taken hold. Unfortunately there are no treatments that can stop or slow the progression. Accurate tools are needed to diagnose the condition earlier and to understand the disease process involved in more depth.

In Alzheimer's disease two proteins, beta-amyloid and tau form small abnormal clumps called amyloid plaques and neurofibrillary tangles. These are seen throughout the brain, severely affecting two connected regions, the hippocampus and the entorhinal cortex. Our studies have revealed that an area known as the presubiculum that lies between them, also involved in memory, appears to be protected from nerve cell damage. Interestingly, amyloid plaques are absent and there is significantly less tau.

Here at the QSBB, samples of the presubiculum and the entorhinal cortex were dissected using a high powered laser and a technique performed to measure and compare any variations in the amount of proteins in these locations. Differences were found not only in the quantity, but also in the way they behaved.

We continue to investigate whether the proteins look promising targets for early diagnosis. Our aim is to see if changes are also apparent in cerebrospinal fluid, the fluid that surrounds our brain and spinal cord, which can be obtained during life. This could aid earlier accurate diagnosis and may open avenues for potential treatments.

Image right: Microscope images highlighting the differences between the presubiculum area (outlined in red) which has significantly less tau pathology than the entorhinal cortex (outlined in yellow). The presubiculum has diffuse cloud-like staining of amyloid and the entorhinal cortex has clumping of dense amyloid plaques.

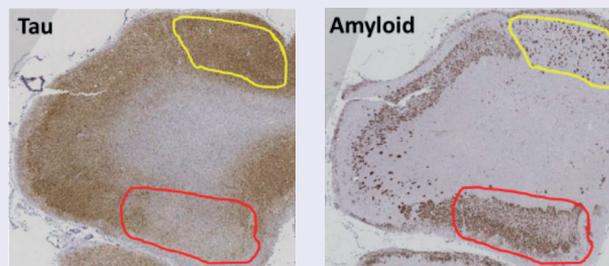
Dr Conceicao Bettencourt, Research Associate and Professor Janice Holton, Neuropathologist are investigating DNA methylation alterations in multiple system atrophy:

Multiple system atrophy (MSA) is a neurodegenerative illness causing balance abnormalities, slow movements and stiffness. At present there are no effective treatments to halt or delay disease progression and no tests available to provide an accurate diagnosis in life. Lumps of a sticky protein called alpha-synuclein form in brain cells of affected individuals leading to death of nerve cells in specific areas of the brain. The reasons for this are not fully understood.

We know that cells depend on several things to correctly produce proteins. DNA provides the code, a sequence of letters for different proteins to be made. This sequence is the same in all cells of the body. Cells therefore require additional instructions to know whether they need to behave as, for example, a blood cell or a nerve cell. These instructions are given by chemical modifications to the DNA and include a change called DNA methylation which works like a dimmer switch to vary the amount of proteins produced by each cell. Recent studies have shown that DNA methylation plays an important role in some neurodegenerative disorders, but this has not been studied in MSA before.

Analysis of samples from donors with neuropathologically confirmed MSA to see if harmful changes to DNA methylation arise revealed considerable differences between MSA and healthy brain tissue and pointed to proteins that may be contributing to malfunction and death of nerve cells.

Because DNA methylation is potentially reversible with appropriate drugs, knowing where the damage occurs is important. If it is detected early it could improve diagnosis, aid development of biomarkers to monitor the disease in life and measure response to treatments in future drug trials.





Dr Zane Jaunmuktane who has worked at QSBB since 2017 and is supported by the Department of Health's NIHR Biomedical Research Centre's funding scheme, reveals her life as a neuropathologist, a medically trained doctor specialising in diseases of the nervous system:

What inspired you to become a neuropathologist?

When I was nine years old I contracted meningococcal meningitis, a life-threatening infection of the brain and spent over a month in hospital. My interest in medicine, specifically neurology, began there. Whilst in medical school I joined a research programme in a neuropathology laboratory. I found pathology studies fascinating, hence it was a natural decision to become a neuropathologist.

How long did it take to get to this position?

It took me seventeen years to become Clinical Lecturer at QSBB, there is so much to learn about the human body.

What is the most interesting aspect of your work?

It is the regular surprises we come across when examining brain tissue. Over recent decades many great advances have been made in diagnosing neurological illnesses based on radiology or examination of body fluids. Yet frequently we see changes in the brain that were not suspected in life. It is always thrilling to shed light on the reasons why a devastating disease developed or determine the exact condition a patient had.

Are we nearer to unravelling the mysteries of neurodegenerative illnesses? Because of their complexity, they are one of the greatest challenges in medicine. Many mysteries have been solved over the last hundred years since the first descriptions of diseases such as Alzheimer's and Parkinson's. Whilst I do not know when we will defeat even one of these, I think the time is certainly getting closer.

When you are not examining brains, what do you enjoy doing? I find long distance walking relaxing, I recommend it to everyone! I also take every opportunity to visit my family who live over a thousand miles away. My two sisters and I share an enthusiasm for fashion and how it evolves over time.

Which scientist would be your fantasy dinner guest?

I would love to have met the neuropathologist Dorothy Russell. Following the death of her parents she had to move from Australia to England in 1904 to live with relatives and in 1946 became a Professor of Pathology in London. I think she was a remarkable woman and a dinner with her would have been a real treat!

If you had not become a neuropathologist, what would you have been? Had I not been bitten by the neuropathology bug, which I am very grateful for, I would certainly have specialised in another area of neurology.

Contributors



Contributors from left to right: (top row) Dr Rina Bandopadhyay, Dr Eduardo Fernandez, Dr Christina Toomey, Dr Tammaryn Lashley, Dr Conceicao Bettencourt, Professor Janice Holton.

Contributors from left to right: (lower row) Dr Zane Jaunmuktane, Ms Karen Shaw, Brain Bank Nurse and editor of *Brain Matters*.

Donations



Coordinators from left to right:
Lynn Haddon and Robert Courtney

Brain donation coordinators

QSBB administrator, Lynn Haddon is often the first point of contact for potential donors. Lynn coordinates the brain donor scheme and along with Robert Courtney, senior technician, arranges the safe receipt of donated tissue.

The team liaise with relatives, hospital staff, funeral directors and couriers, to ensure the careful donation of the brain 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 on 020 7837 8370
l.haddon@ucl.ac.uk**

The cover image shows a design interpretation of microglia.

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 and several other benefactors, in particular the Virginia Keiley Benefaction.

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

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