Alcoholism research that won't break the bank

A pioneering project at the University of Sydney is storing donated brain tissue from alcoholics and healthy control populations to provide researchers with a wealth of samples. **Professor Jillian Kril** and colleagues at the New South Wales Brain Tissue Resource Centre (NSW BTRC) are using this resource to make significant advances in the understanding of alcohol-related brain damage.

Alcohol-related disorders are areas of major public health and socio-economic concern. Research aimed at understanding addiction and organ damage, especially alcohol-related brain damage (ARBD), must be underpinned by a sound knowledge of the biology behind alcohol abuse at a cellular level.

Understanding the biological basis of addiction, and the factors affecting an organ's susceptibility to damage, is required to further our knowledge of alcoholism and alcohol toxicity – and for the development of treatment and prevention strategies. Such research is dependent on access to high quality, extensively characterised tissue from alcoholic subjects and matched controls.

OPENING THE BANK ACCOUNT

The New South Wales Brain Tissue Resource Centre (NSW BTRC) at the University of Sydney is an established brain bank that focuses on facilitating research into alcoholism, alcohol-related brain damage and associated conditions. The aim of this innovative facility is to provide fresh-frozen and formalin-fixed tissue to research groups worldwide who study alcohol use disorders.

Tissue is collected, with appropriate consent, from forensic autopsies and through a prospective brain donor programme called 'Using our Brains'. The donors have lifestyle, medical and psychiatric histories fully documented to provide the maximum benefit to future researchers.

OPEN ACCESS BANKING

Access is open to any researcher with institutional ethics approval. Since its inception, the NSW BTRC has provided tissue for over 150 research projects, predominantly from the USA, Europe and Australia. More than 180 publications have arisen from these projects, and Professor Kril has been involved in many of these with colleagues at the University of Sydney.

Using tissue samples from the bank, she and her fellow researchers have uncovered where in the brain chronic alcohol use causes the most damage – consequently revising the previous understanding of ARBD, based on animal models of alcohol use.

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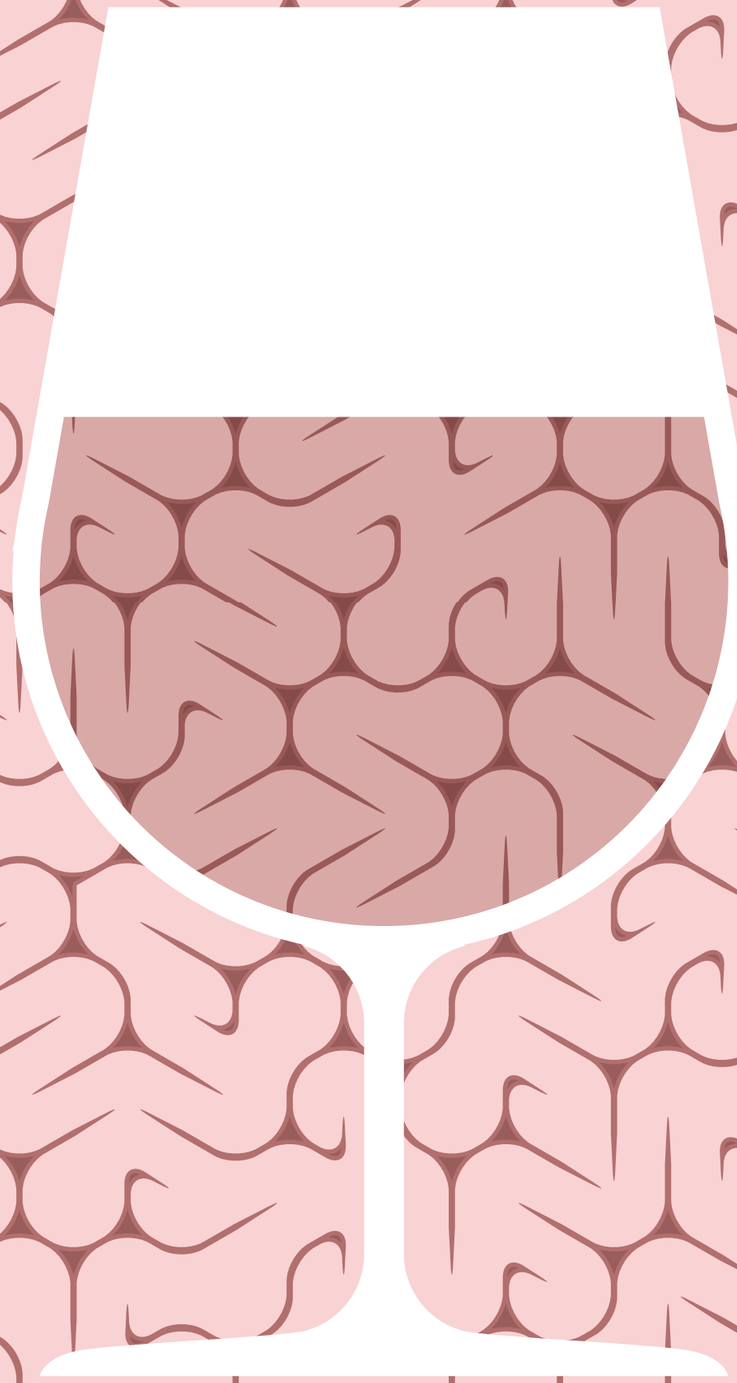
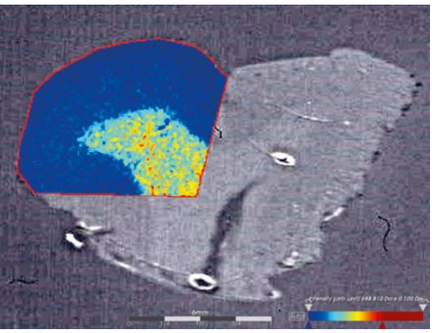
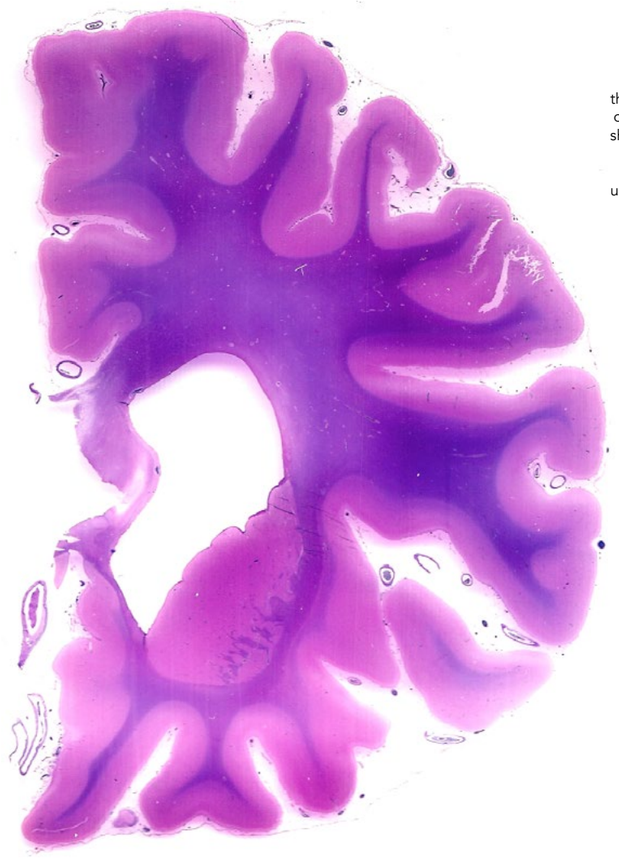




Matrix Assisted Laser Desorption/Ionization (MALDI) imaging of a section of the inferior temporal gyrus shows clear differentiation of the grey matter and white matter based on chemical (lipid) composition. *Source Mr Caine Smith, University of Sydney.*



A coronal section through the frontal lobe of the right hemisphere shows, from the outside inwards, the cerebral cortex (stained pink), underlying white matter (stained blue), the fluid filled cavity of the lateral ventricle and the adjacent caudate nucleus. *Source NSW BTRC.*

In an early study, Professor Kril resolved controversy within the literature which had been unable to find agreement on whether chronic alcohol consumption damaged the cerebral cortex (the largest region of the mammalian brain which plays a key role in memory, attention, perception, cognition, awareness, thought, language, and consciousness).

Using brain samples from carefully screened alcoholics and matched controls, her team's research showed that selective neuronal loss occurred in the prefrontal cortex, but not the primary motor cortex. The cortex is commonly described as comprising three parts: sensory, motor, and association areas. The prefrontal cortex is part of the association areas and is involved in memory, planning and abstract thought. Professor Kril further demonstrated that this neuronal loss was accompanied by a reduction in the volume of white matter in the frontal lobe, a feature which can be identified during life using MRI scans.

THE LIMITS OF MODELLING

The current practice of using animal models of alcoholism to study ARBD had previously indicated that neurogenesis (the development of new neurons within the brain) was a significant aspect of neuronal loss, as sufficient neuron replacement was not occurring. A study by Dr Sutherland, Professor Kril and colleagues in 2013, using material from the brain bank, showed that this effect was not found in the sub-ventricular zone or olfactory bulb of human subjects. This led the researchers to conclude that: "Neurogenic deficits are unlikely to contribute to hyposmia [loss of smell related to brain damage in the olfactory bulb] in chronic alcoholics."

This is just an example of the range of studies which have made use of the tissue, and continue to probe the features of ARBD using this resource. New developments in genetic investigation have provided novel opportunities for further research. The automated analysis of the transcriptome (the sum of all RNA in a cell and a measure of its active genes) has allowed the categorisation of genetic activity in diverse neuronal populations and their comparison in disease states such as ARBD.

GENETIC STUDIES PROBE NEW AVENUES

The provision of high quality samples which have been appropriately stored and characterised is vital to this sort of work. Groups as far away as the University of Texas have used samples from the bank for such studies, successfully identifying the down-regulation of myelin genes (the electrical insulation required for nerve cells to function correctly) as the predominant pathology in ARBD.

Other groups have found similar patterns or used the techniques to investigate other aspects of ARBD, such as addiction. The parts of the brain associated with addictive behaviours were found to be abnormally affected in ARBD samples, most noticeably in the nucleus accumbens. This feeds in to other considerations such as the co-use of drugs,

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Q&A

What most interests you about neuropathology?
The extraordinary complexity of the human brain is endlessly fascinating. Studying brain diseases gives us insights into this complexity. It also teaches us about how the brain works in healthy individuals.

What are the particular strengths of the NSW BTRC?
The breadth of clinical and lifestyle information collected on donors, and made available to researchers, increases the scope of the research that can be undertaken. This, together with the careful pathological screening and attention paid to tissue quality, means the full potential of the donation can be realised.

How can researchers access the samples?
Any researcher, with institutional ethics approval, can apply to access tissue from the resource. Applications are reviewed for scientific merit by independent experts and then tissue prepared to suit the type of research to be undertaken.

What is the most interesting finding to come out of these studies so far?
Demonstrating that neuronal loss can occur in one brain region while other regions, even those immediately adjacent, are spared. The mechanisms that underlie this selective vulnerability are yet to be determined.

What direction do you see alcohol related neuropathology research heading into in the future?
The explosion in 'omics research has only just begun and future studies which can tell us, at a cellular level, what gene or protein is changed in response to alcohol exposure will advance our knowledge greatly.

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and especially nicotine, as 80% of chronic alcoholics smoke cigarettes.

The low rate of use of illicit drugs in the Australian population makes the NSW BTRC a particularly useful resource for investigating this phenomenon. Groups studying these issues have found that both nicotine and alcohol have an effect on the actin pathways, which make the 'skeletal' proteins of a cell. The effects of co-use are different depending on the region of the brain being investigated, leading researchers to conclude that: "Alcohol's effect on cellular architecture is modulated by nicotine co-abuse in a region-specific manner."

A BROAD RESEARCH FIELD

Further research by Professor Kril's team has shown that thiamine deficiency, liver disease and lifetime alcohol consumption all worsen ARBD. This highlights the multifactorial nature of the problem and the desperate need for higher quality research, such as this, to be undertaken. Having collections like the NSW BTRC is essential if this work is to continue to expand its scope and utilise novel techniques.

Professor Kril has over twenty years' experience of human neuropathology research, with more than 175 peer-reviewed publications to her name. As Director of the NSW BTRC and Professor of Neuropathology (as well as Associate Dean (Research) for the Sydney Medical School), she is the ideal person to oversee the vital work that the brain bank is resourcing.

Supported by the University of Sydney, which provides the infrastructure to house the NSW BTRC, and the Deputy Director Dr Greg Sutherland, researchers from across the globe can bank on an expert curation of this important resource.

Detail

RESEARCH OBJECTIVES

Professor Jillian Kril is an internationally recognised research neuropathologist. Her current research looks at furthering our knowledge of alcoholism and alcohol toxicity, by improving understanding for the biological basis of addiction, and the factors affecting an organ's susceptibility to damage.

FUNDING

- National Institute on Alcohol Abuse and Alcoholism (NIAAA)
- University of Sydney

COLLABORATORS

- Greg Sutherland (Deputy Director NSW BTRC, Discipline of Pathology, University of Sydney)
- R Adron Harris and R Dayne Mayfield (Waggoner Center for Alcohol & Addiction Research at The University of Texas at Austin)
- Fulton Crews (University of North Carolina Bowles Center for Alcohol Studies)
- Georgy Bakalkin's group at the Department of Pharmaceutical Biosciences, Uppsala University

BIO

Jillian Kril is Professor of Neuropathology and Associate Dean (Research) for the Sydney Medical School at The University of Sydney. She has over 20 years' experience in human neuropathology. Her research examines the extent and topography of neuronal loss and degeneration in ageing, alcoholism and dementia, and has yielded over 175 peer-reviewed publications.

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