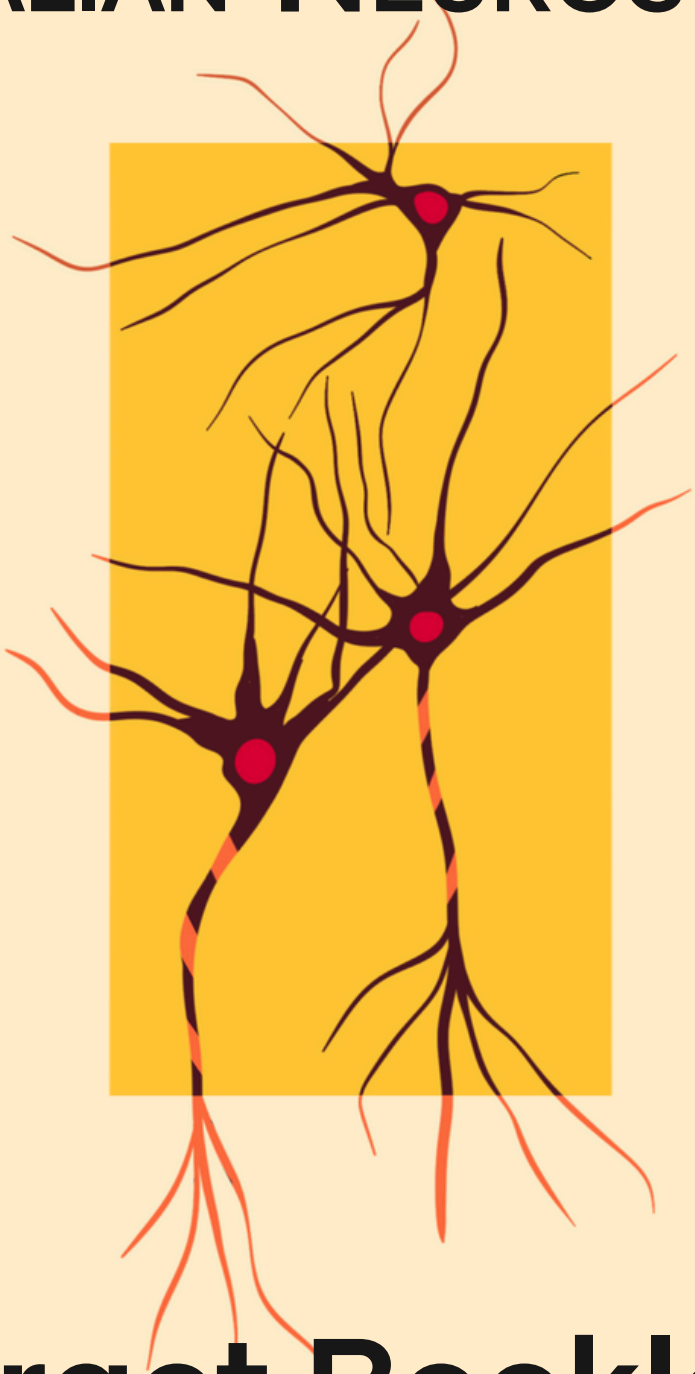
# Symposium of Western Australian Neuroscience



# Abstract Booklet 2025

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Symposium of
Western Australian
Neuroscience

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# HOW TO GET THERE

## VENUE

**T.L. Robertson Library (B105)** - Curtin University | *Kent St., Bentley, 6102.*

SWAN 2025 will be held across Levels 4 & 7 in the function spaces.
To access a full campus map, see: Curtin Campus Maps.

TL Robertson Library is accessible by wheelchair & contains wide lifts for access between levels. A parenting room is located on Level 2 – please speak to a staff member if you don't have a Curtin ID card & would like to access the room.

## PUBLIC TRANSPORT

Plan your journey with Transperth! We encourage attendees to use public transport to Curtin as it's affordable & reduces emissions! Curtin has two bus stations: Curtin Central (CC) & Curtin University (CU).

From the *Canning Bridge Station* **(Mandurah-Perth Line)**, take **Bus 100 or 101** (Stand 3) to *CC Stand 9* / *CU Stand 4*, buses run every 7-8 minutes during peak times. Return via **Route 100**: *CC Stand 5* / *CU Stand 5* or **Route 101**: *CC Stand 10* / *CU Stand 2*. Note: not all Mandurah-bound trains stop at Canning Bridge.

From the *Oats Street Station* **(Armadale Line)**, take **Bus 998** (Stand 1) to *CU Stand 1* & return via **Bus 999** from *CU Stand 8*. Routes 998/999 do not stop at Curtin Central.

## PARKING

If you do choose to drive to Curtin, parking bays are colour-coded and divided into 5 zones, with varying rates & access conditions. Payments are made via the CellOPark app.

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*Green Zone*: $0.84 per hour (maximum $4.20 per transaction)
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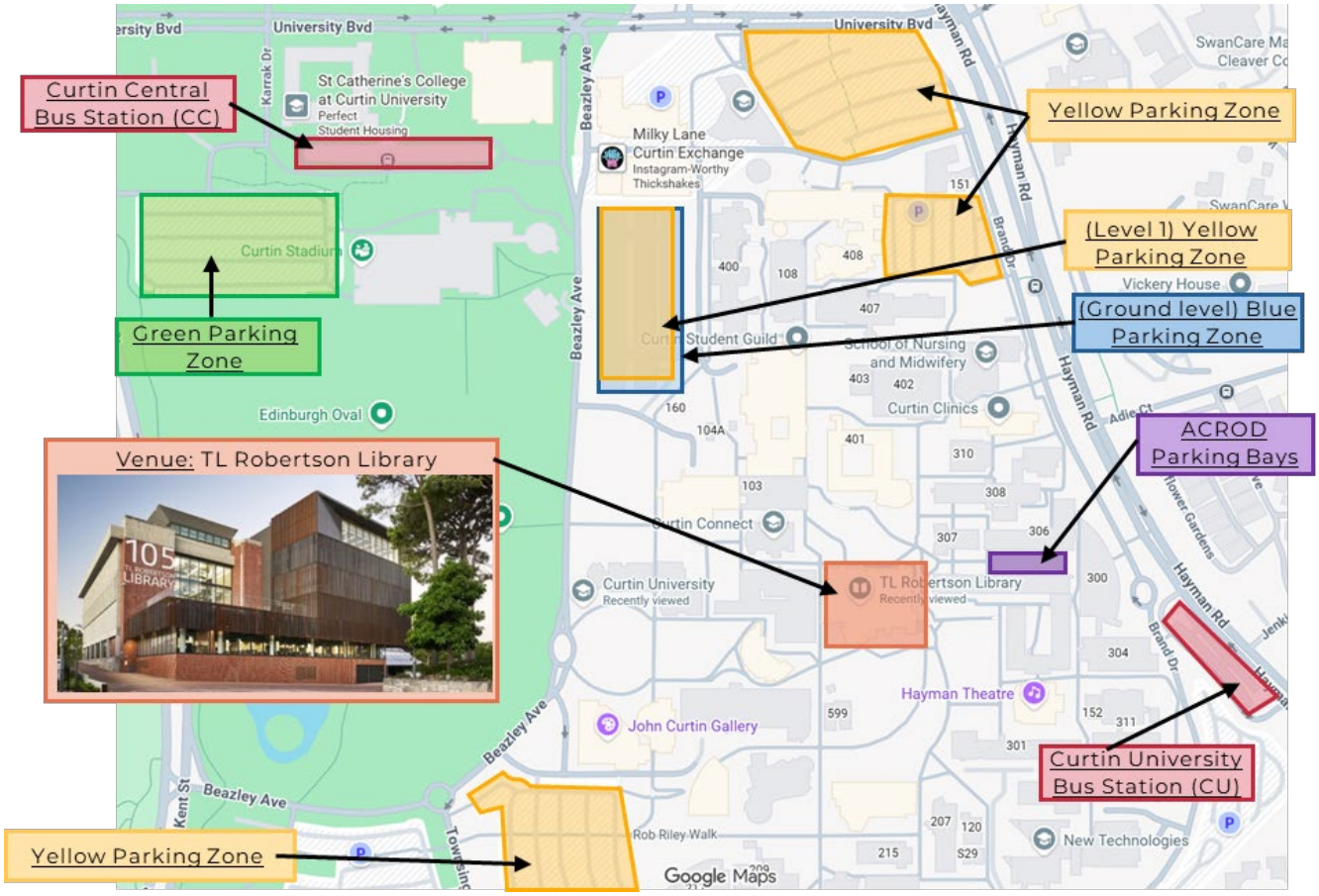

# PROGRAM

**Registration** (L7)
08:20

**Welcome at the Lantern** (L7)
08:50 – 09:00

***Morning Plenary*: Sarah Hellewell** (The Lantern, L7)
09:00 – 09:40

***Session 1*: Acquired Brain Injury and Recovery** (The Lantern, L7)
09:40 – 10:50

**Andre Avila**
The Application of Magnetic Resonance Spectroscopy in Assessing Neurocognitive and Neuroinflammatory Outcomes in mTBI and PPCS

**Jacinta Thorne**
Association between cerebral blood flow, cardiovascular parameters and symptoms following mild traumatic brain injury: an exploratory arterial spin labelling study

**Sophie Catchpole**
Characterising the impact of childhood stroke on brain development in mice

**Leah Dempsey**
Associations between Sleep Hygiene Factors and Sleep Health in Community Dwelling Individuals with an Acquired Brain Injury

***Morning Tea***
10:40 – 11:05

***Session 2*** (The Lantern, L7) and ***Session 3*** (L4, 434)
11:05 – 12:20

## *Session 2*
Neural Connectivity, Stimulation and Cellular Models

**Grace Bliesner**
Intervention for Persisting Post-Concussive Symptoms after Mild Traumatic Brain Injury

**Adel Asanalieva**
Characterising neuronal populations activated during non-invasive intermittent theta burst stimulation (iTBS) using the Tet-off-pRAM viral system in mice.

**Ruvindu Kaluarachchi**
Directed Brain Connectivity during Motor Imagery: Insights from EEG and NIRS using Transfer Entropy

**Alexandra O'Brien**
Reciprocal connectivity of the auditory thalamus and thalamic reticular nucleus in the guinea pig.

**Joey Lye**
Characterisation of inner ear organoids derived from USH2A patient induced pluripotent stem cells.

## *Session 3*
Genetics, Metabolism and Molecular Mechanisms in Brain Disease

**Anika Lamisa**
Exploring shared genetic architecture between Alzheimer's Disease and Diabetes-related metabolic biomarkers

**Olasunkanmi Bamidele**
Gene overlap, local genetic correlation, and clinical validation of shared genes between Alzheimer's disease and chronic pain-related disorders

**Ayeisha Milligan Armstrong**
What we are learning about Alzheimer's disease from genes in the brain's cleaning system

**Kate Gilbert**
Therapeutic potential of targeting the metabolism pathway in degenerating photoreceptors in mouse models of retinitis pigmentosa

**Miya Sandesh**
Evaluating the effect of histone deacetylase inhibition in the Cnga3-/- mouse model of achromatopsia

# PROGRAM

**Lunch (L7)**
12:20 – 13:10

**A brain exercise interlude with Prof Ken Nosaka**
13:10 – 13:25

***Session 4*** (L4, 434) & ***Session 5*** (The Lantern L7)
13:30 – 14:30

| ***Session 4*** Behaviour, Perception and Outcomes in Brain Disorders | ***Session 5*** Cancer, Metabolic Health and Cognition |
|---|---|
| **Jacinta Thorne** Predicting recovery outcomes following mild traumatic brain injury in an Australian community-based population: results from the Concussion Recovery Study (CREST) | **Ken Nosaka** Effects of eccentric versus stretching exercise training on cognitive function of older women |
| **Cassandra Brooks** Characterising the appearance and perceived severity of visual snow | **Helena Bertazzo** Late Effects of Radiation in a Juvenile Preclinical Model of Paediatric Brain Cancer |
| **Reece Granger** An observational Study of Head Injury Assessments and Mechanisms of Head Impact in Australian National Rugby League | **Desiree Sexauer** Blood-based biomarkers for the detection of melanoma brain metastasis |
| **Kym Wansbrough** No difference in muscle coactivation during submaximal plantarflexion contractions in individuals with Multiple Sclerosis compared to matched controls | **Amy Woodfield** Changes in fasting plasma insulin, fasting plasma glucose and insulin resistance are associated with longitudinal cognitive function. |

**Afternoon Tea** (L7)
12:20 – 13:10

**Afternoon plenary: Lindy Rae at the Lantern** (L7)
14:55 – 15:35

**Career Pannel discussion**
15:35 – 16:20

| **Dr Liz Dallimore** | **Dr Gill Cowan** | **Dr Gurkiran Kaur Flora** | **Mr John Fitzgerald** | **Prof Ryan Anderton** |
|---|---|---|---|---|
| *CEO & Managing Director for Argenica Therapeutics* | *General Practitioner, Sports Doctor & Senior Clinical Research Fellow* | *Senior Coordinator at Health Support Services (WA Health System)* | *Chief Advancement Officer & Principal Consultant at Orimco* | *Head of Discipline at the University of Notre Dame Australia* |

**Official close & sundowner on the Terrace** (L4)
16:30
Award Presentations at 17:15

**Symposium End**
19:00

# PLENARY SPEAKERS

## DR SARAH HELLEWELL

Dr Sarah Hellewell is a Senior Research Fellow in Neurotrauma and Stan Perron People Fellow at Curtin University and the Perron Institute in Perth, where she is deputy lead of the Neurotrauma research group and leads a team of 17 researchers.

She is the top-ranked expert in traumatic brain injury in Western Australia and in the top 0.4% of experts worldwide, and has received more than $15M in funding as CI to support her work. Her research spans subconcussive to severe brain injury in the general population, athletes and military personnel. She uses multimodal MRI, fluid biomarkers and functional tests to understand how traumatic brain injury can alter brain structure and function, and how this translates to cognitive and neuropsychological outcomes. She runs several clinical and preclinical projects to translate findings bench to bedside and back again.

### *Morning Plenary Speech:*

**Traumatic brain injury: pathology, outcome and novel therapeutics**

## PROFESSOR CAROLINE (LINDY) RAE

Caroline (Lindy) Rae is Chair of Brain Sciences at UNSW in the School of Psychology, and a senior principal scientist at Neuroscience Research Australia. She is director of NeuRA Imaging, a research-focused MRI facility which is part of the National Imaging Facility.

She has published >160 research papers, including some that did not use magnetic resonance. Her research focusses on determining the relationships between brain biochemistry and brain function. In addition to study of normal brain function her research includes sleep disorders, neuropharmacology, pain, brain congenital and neurological disorders. She is involved in the development of new magnetic resonance applications and analyses such as MR spectroscopy and, more recently, a new method for non-invasive measurement of tissue electrical properties which has static and functional applications.

She has held several Fellowships over her career, including the Oxford Nuffield medical Fellowship, and NHMRC RD Wright and SRFs. She is Past-President of the International Society for Neurochemistry and was awarded the Medal of the Australian and New Zealand Society for Magnetic Resonance (2017) for outstanding contributions to magnetic resonance

### *Afternoon Plenary Speech:*

**Quantitative mapping of brain activity with electrical conductivity imaging**

# CONTENTS

# Perron Institute

## Leaders in innovative neuroscience research and patient care

One in three people globally live with a neurological condition. Many of these conditions have no effective treatment and we are working to create a future of personalised, precision medicine by tackling these areas of unmet need. We operate statewide specialist neurological services and connect clinicians, researchers, industry and communities to develop new methods of diagnosis, treatment, and prevention, improving the lives of people with neurological conditions.

## Our clinics

The Perron Institute for Neurological and Translational Science conducts neurological subspecialty clinics under a service agreement with North Metropolitan Health Service, connected with WA Health via Sir Charles Gairdner Hospital in the QEII precinct.

### 4,400

**Patient visits (2025) providing:**

- Continuity of care for highly complex cases
- Reduced inpatient and outpatient burden
- Specialised nursing support
- Reduced wait time
- Access to clinical trials and research

### 23+

**Subspecialty clinics including:**

- Parkinson's
- Multiple Sclerosis
- Motor Neurone Disease
- Epilepsy in Pregnancy
- Refractory Epilepsy
- Movement Disorders
- Neuromuscular
- Neurogenetic

### 12

**Consultant Neurologists who work across several hospitals:**

- Sir Charles Gairdner Hospital
- Fiona Stanley Hospital
- Royal Perth Hospital
- St John of God Midland Public Hospital
- Joondalup Health Campus

### 29

**Clinical Trials in 2025–2026**

Involved in setting up or leading:

- 14 Pharmaceutical Clinical Trials
- 15 Investigator Led Clinical Trials

## Research collaboration

### 454
**Research Institutes**

### 44
**Countries**

### 55+
**PhD and Honours students**

### 147
**Publications (2024)**

### 6
**Patents (2024)**

### 40
**Grants (2024)**

### 16
**Research groups**

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# SPEAKER ABSTRACTS

## SESSION ONE
## Acquired Brain Injury & Recovery

### Association between cerebral blood flow, cardiovascular parameters and symptoms following mild traumatic brain injury: an exploratory arterial spin labelling study

**Jacinta Thorne[1,2,3], Sarah Hellewell[2,3], Gill Cowen[3,4,6], Michael Bynevelt[5], HuiJun Chih[6], Anoek van Houselt, Aleksandra Gozt[2,3], Andre Avila[2,3,4], Caerwen Beaton[2,3,4], Melissa Papini[2,3,4], Francesca Buhagiar[7], Amanda Jefferson[4], Elizabeth Thomas[6,8], Alexander Ring[1,9], Antonio Celenza[10,11], Glenn Arendts[11,12], Melissa Licari[13], Dan Xu[4,6,14], Stephen Honeybul[15], Suzanne Robinson[16], Carmela Pestell[1,7], Daniel Fatovich[17,18] and Melinda Fitzgerald[2,3]**

[1]School of Allied Health, Faculty of Health Sciences, Curtin University | *Bentley, WA 6102, Australia*
[2]Perron Institute for Neurological and Translational Science | *Nedlands, WA 6009, Australia*
[3]Curtin Health Innovation Research Institute, Curtin University | *Bentley, WA 6102, Australia*
[4]Curtin Medical School, Faculty of Health Sciences, Curtin University | *Bentley, WA 6102, Australia*
[5]The Neurological Intervention & Imaging Service of Western Australia at Sir Charles Gairdner Hospital | *Nedlands, WA 6009, Australia*
[6]School of Population Health, Curtin University | *Bentley, WA 6102, Australia*
[7]School of Psychological Science, The University of Western Australia | *Nedlands, WA 6009, Australia*
[8]Medical School, The University of Western Australia | *Nedlands, WA 6009, Australia*
[9]Institute for Immunology and Infectious Diseases, Murdoch University | *Murdoch, WA 6150, Australia*
[10]Emergency Department, Sir Charles Gairdner Hospital | *Nedlands, WA 6009, Australia*
[11]Division of Emergency Medicine, Anaesthesia & Pain Medicine; School of Medicine, The University of Western Australia | *Nedlands, WA 6009, Australia*
[12]Emergency Department, Fiona Stanley Hospital | *Murdoch, WA 6150, Australia*
[13]The Kids Institute Australia | *Nedlands, WA 6009, Australia*
[14]The First Affiliated Hospital, Sun Yat-Sen University | Guangzhou, China
[15]Department of Neurosurgery, Sir Charles Gairdner Hospital & Royal Perth Hospital | Perth, WA 6000, Australia
[16]School of Health and Development, Deakin University | Melbourne, VIC 3125, Australia
[17]Emergency Medicine, Royal Perth Hospital | *Perth, WA 6000, Australia*
[18]Centre for Clinical Research in Emergency Medicine, Harry Perkins Institute of Medical Research | *Nedlands, WA 6009, Australia*

Following mild traumatic brain injury (mTBI) some individuals experience heart rate (HR) alterations and exercise intolerance. It is postulated these alterations are related to autonomic nervous system dysfunction and impaired cerebral blood flow (CBF), yet the neurobiological mechanisms remain unclear. This study examined the relationship between CBF in brain regions aligned with autonomic control, cardiovascular parameters and symptom presentation in individuals following mTBI.

Prospective observational study of 30 adults aged 18-65 years within ten days of mTBI, and 33 age- and sex-matched controls. Pseudo-continuous arterial spin labelling MRI was used to examine CBF in brain regions recognised for their role in cardiovascular autonomic response (insular cortex, anterior cingulate cortex (ACC) and amygdala). Resting HR, exercise tolerance (Buffalo Concussion Bike Test), and self-reported symptoms (Post-Concussion Symptom Scale) were assessed with respect to CBF in each region.

Resting HR ($p=0.042$) and HR change during exercise ($p=0.004$) were significantly lower for mTBI participants than controls. CBF was increased in the right insula ($p=0.027$) and right amygdala ($p=0.025$) in people who had recently sustained mTBI compared to controls. A positive association between resting HR and CBF in the right ACC ($r=0.423$, $p=0.016$) was identified for controls, but not mTBI participants. Similarly, a positive association was observed between CBF in the right ACC and both symptom severity and autonomic-type symptoms in controls, but not following mTBI.

This exploratory study provides preliminary evidence that the natural regulatory relationship between CBF, resting HR, and symptomology is disrupted following mTBI, with the anterior cingulate cortex identified as an important region of interest.

## The Application of Magnetic Resonance Spectroscopy in Assessing Neurocognitive and Neuroinflammatory Outcomes in mTBI and PPCS

**André N. Avila[1,2,3], Grace Bliesner[2,3], Melissa G. Papini[1,2,3], Caerwen S. Ellery[1,2,3], Ruby Gilroy[1,2,3], Melinda Fitzgerald[1,2,3], Sarah C. Hellewell[2,3,4]**

[1]Curtin Medical School, Curtin University | *Bentley, WA 6102, Australia*
[2]Curtin Medical Research Institute, Curtin University | *Bentley, WA 6102, Australia*
[3]Perron Institute for Neurological and Translational Science | *Nedlands, WA 6009, Australia*
[4]Centre for Neuromuscular & Neurological Disorders, University of Western Australia | *Crawley, WA 6009, Australia*

Metabolic dysfunction and neuroinflammation are central to mild traumatic brain injury (mTBI) and may contribute to persistent post-concussion symptoms (PPCS). Proton magnetic resonance spectroscopy ($^1$H-MRS) enables non-invasive assessment of neurometabolic alterations and may enable greater understanding of PPCS and its associations with cognitive and inflammatory outcomes. This systematic scoping review used PRISMA-ScR guidelines to synthesise data from studies using $^1$H-MRS in mTBI and PPCS, focusing on links to cognition and inflammation.

A comprehensive literature search was performed across six databases. Eligible studies included clinical or preclinical research on mTBI or PPCS, employing $^1$H-MRS and reporting cognitive and/or inflammatory outcome measures. Screening and data extraction were performed independently by multiple reviewers using Covidence.

32 studies met inclusion criteria: 25 clinical, seven preclinical. Cognitive outcomes were assessed in 24 human studies and 4 animal studies; inflammation was assessed in one human and six animal studies. Most human studies focused on PPCS (n=11), followed by acute mTBI (n=9), and mixed timepoints (n=5). N-acetylaspartate (NAA) was the most commonly reported metabolite (n=29), followed by choline (Cho, n=24) and creatine (Cr, n=22). NAA reductions were the most consistent finding (n=14), and were associated with reduced cognitive function. Associations between other metabolites (e.g., Cre, Cho) and cognition were reported in 9 studies, with no clear pattern. One study reported a negative association between IL-6 and total-NAA.

Clear relationships between NAA reductions in mTBI/PPCS and cognitive deficits exist, though further standardised, multimodal studies are needed to clarify associations of other metabolites and explore links with inflammatory markers.

## Characterising the impact of childhood stroke on brain development in mice

**Sophie Catchpole[1], Emily King[1,2], Hakuei Fujiyama[3], John N.J Reynolds[4], Jamie Beros[1,2], Alex Tang[1,2]**

[1]Experimental & Regenerative Neurosciences, The University of Western Australia | *Crawley, WA 6009, Australia*
[2]Perron Institute for Neurological and Translational Sciences | *Nedlands, WA 6009, Australia*
[3]School of Psychology, Murdoch University | *Murdoch, WA 6150, Australia*
[4]Department of Anatomy and the Brain Health Research Centre, The University of Otago | *Dunedin, 9016, New Zealand*

Childhood stroke causes lifelong neurological impairment in over 50% of patients, severely impacting quality of life. To date, very little is known on the impact of stroke in developing neural circuits and consequently, there are no treatments tailored specifically to childhood stroke. A potential therapeutic target for childhood stroke is the axon initial segment (AIS), a neuronal microdomain responsible for neuronal excitability that undergoes critical structural refinement during development. The AIS becomes dysfunctional following adult stroke, however, changes to this structure have not been characterised following childhood stroke. Therefore, we investigated the acute and long-lasting changes to the AIS of neurons in the visual cortex following a unilateral ischaemic stroke at P22 in mice. To assess acute changes, tissue was collected at P28 and processed for immunofluorescence of AIS structural proteins and voltage gated sodium ion channels. Long-lasting AIS changes were investigated by transfecting mice with an adeno-associated virus for jRGeco1a and *in vivo* calcium imaging performed on P69, prior to tissue collection and immunofluorescence at P70. Preliminary analysis suggests that one week after childhood stroke, the AIS shortens by ~3.4µm and becomes irregular in shape at the peri-infarct cortex compared to the contralesional hemisphere and sham controls. These results suggest that the AIS undergoes maladaptive structural changes post-stroke which may underlie long-lasting impairments to neuronal excitability. Therefore, targeting AIS dysfunction following childhood stroke may serve as a novel therapeutic target to prevent long-term disability.

## Associations between Sleep Hygiene Factors and Sleep Health in Community Dwelling Individuals with an Acquired Brain Injury

**Leah Dempsey[1,2], Philipp Beranek[1,2], Travis Cruickshank[1,2,3], Mitchell Turner[1,2]**
[1]Centre for Precision Health, Edith Cowan University | *Joondalup, WA 6027, Australia*
[2]School of Medical and Health Sciences, Edith Cowan University | *Joondalup, WA 6027, Australia*
[3]Perron Institute for Neurological and Translation Research | *Nedlands, WA 6009, Australia*

The association between sleep health and sleep hygiene factors have been under-researched in community dwelling individuals with an acquired brain injury (ABI). Poor sleep in individuals recovering from an ABI is linked to higher levels of anxiety and depression, while also being associated with poorer motor outcomes and slow functional recovery. Understanding the factors contributing to poor sleep is therefore imperative.

This research examined, for the first time, associations between sleep health and sleep hygiene factors, using the Sleep Health Index and the Sleep Environment Questionnaire in individuals with an ABI between the age of 18-65. No significant association was observed between sleep hygiene factors and sleep health. However, when compared to normative values in the general population, this sample had poor sleep quality, disordered sleep and lower overall sleep health values.

The results from this study are not consistent with research in other populations that show sleep hygiene factors are associated with sleep health. Sleep hygiene interventions have the potential to be a low-cost intervention for sleep health. Larger more consistent studies are needed to determine what does and does not impact sleep health in the ABI population. This is of importance due to the impact good sleep health has on quality of life in this population.


# Centre for Precision Health

The Centre for Precision Health (CPH) is an Edith Cowan University Strategic Research Centre. We aim to optimise health and quality of life through cutting-edge research that delivers impactful precision health solutions. Our researchers are focused on applying a precision health model across three strategic domains including biomarker discovery, disease mechanisms, and health translation.

The Centre has specialised pieces of research infrastructure including the GeneTitan, for all your genome-wide genetic analysis needs, and much more and can be accessed through research collaboration or service provision.

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# SESSION TWO
# NEURAL CONNECTIVITY, STIMULATION & CELLULAR MODELS

## Intervention for Persisting Post-Concussive Symptoms after Mild Traumatic Brain Injury

**GRACE BLIESNER[1,2], ANDRE AVILA[1,2], CAERWEN ELLERY[1,2], MELISSA PAPINI[1,2], KIERAN EDMUNDS[1,2], BLAKE RIPPON[1,2], HARDI VYAS[1,2], JACINTA THORNE[1,2], AMANDA JEFFERSON[1,3], MELINDA FITZGERALD[1,2], SARAH HELLEWELL[1,2,4]**
[1]Curtin Medical Research Institute, Faculty of Health Sciences, Curtin University | *Bentley, WA 6009, Australia*
[2]Perron Institute for Neurological & Translational Science | *Nedlands, WA 6009, Australia*
[3]Curtin Medical School, Faculty of Health Sciences, Curtin University | *Bentley, WA 6009, Australia*
[4]Centre for Neuromuscular and Neurological Disorders, University of Western Australia | *Crawley, WA 6009, Australia*

Mild traumatic brain injury (TBI) accounts for approximately 80% of all TBI cases worldwide. 20-50% of people remain symptomatic beyond three months, termed 'persisting post-concussion symptoms' (PPCS). There are limited treatment options for the underlying brain dysfunction associated with by PPCS. Electroencephalography (EEG)-guided neurofeedback is a non-invasive method to modulate brain activity and has shown efficacy in reducing symptoms in small-scale studies. The aim of this randomised clinical trial is to determine efficacy of neurofeedback for PPCS and elucidate biological mechanisms of action which may underlie symptom reduction. This study combines multiple lines of investigation to determine the efficacy and mechanisms of neurofeedback, including blood and saliva biomarkers; 3-Tesla MRI scans, quantitative EEG, cognitive assessment and self-reported symptom questionnaires. Following baseline assessment, participants are randomised into one of three groups: neurofeedback, concentration training (environmental control) or no-training control. Neurofeedback and concentration groups undergo 18 sessions of EEG-guided (or non-guided) training (3x/week). Assessments described above are repeated for all participants to compare individual response (delta change) and differences at the group level (repeated measures ANOVA) to determine whether neurofeedback is more effective than control. The study is ongoing, with 27/45 participants recruited to-date (60% of target). Recruitment is expected to be finalised Q4 2025. This study will determine whether neurofeedback training alters PPCS symptoms compared to in environmental and no-training control conditions and determine for the first time whether biological changes underlie changes in symptom reports. If found to be effective, neurofeedback could be a viable, low-cost treatment strategy to reduce the biological and symptomatic sequelae of PPCS.

## Characterising neuronal populations activated during non-invasive intermittent theta burst stimulation (iTBS) using the Tet-off-pRAM viral system in mice

**ADEL ASANALIEVA[1], JAMIE BEROS[1], JENNIFER RODGER[1]**
[1]Perron Institute for Neurological and Translation Research | *Nedlands, WA 6009, Australia*

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive method of brain stimulation that is used as an intervention in treatment resistant depression. rTMS is typically delivered to the prefrontal cortex (PFC) to modulate brain activity and induce neuroplasticity in associated brain regions implicated in emotional regulation. However, despite its widespread adoption and clinical efficacy, the cellular mechanisms underlying this treatment remain poorly understood. Specifically, it is unclear which neuronal populations are activated during stimulation and where they are located in the PFC.

This project uses an activity-dependent viral labelling strategy (pRAM) in a mouse model to investigate neuronal activation following intermittent theta-burst stimulation (iTBS), a commonly used excitatory rTMS protocol. Adult mice received a unilateral PFC injection of the Tet-off-pRAM-mScarlet viral construct which causes activated neurons to express an mScarlet fluorophore. Suppression of viral expression was achieved with tetracycline food supplementation until the day before stimulation to restrict expression to the stimulation window. Animals received either a once off iTBS (192 seconds, 1800 pulses) or time matched sham stimulation to the PFC and perfused 48 hours later.

Data quantification and analysis is currently ongoing, but we have validated that the pRAM virus resulted in successful fluorophore expression in the PFC, and that this was reduced in control animals that were not removed from tetracycline food supplementation. Using this system, we hypothesise that iTBS will result in an increased number of labelled neurons in the PFC compared to sham stimulated animals. This study provides important insights into the cellular mechanisms of rTMS.

## Directed Brain Connectivity during Motor Imagery: Insights from EEG and NIRS using Transfer Entropy

**Ruvindu Kaluarachchi, Hanieh Bhakshayesh[1], Tele Tan[1], Darren Beales[2]**
[1]School of Elec Eng, Comp and Math Sci (EECMS), Faculty of Science and Engineering, Curtin University | *Bentley, WA 6102, Australia*
[2]Curtin School of Allied Health, Faculty of Health Sciences | *Bentley, WA 6102, Australia*

Motor imagery (MI), the cognitive rehearsal of movement without overt execution, engages cortical networks that overlap with those activated during actual motor execution. This ability to simulate motor actions supports neuroplasticity and positions MI as a key tool for rehabilitation and brain computer interface (BCI) development. A more precise understanding of how cortical regions interact during MI is critical to advancing these applications.

This study investigated directed connectivity during left- and right-hand MI using a multimodal dataset combining electroencephalography (EEG) and near infrared spectroscopy (NIRS) from 29 healthy participants. Transfer Entropy (TE) was applied to quantify directional information flow, while Conditional Mutual Information (CMI) controlled for shared influences and indirect pathways, strengthening the interpretation of direct interactions. Statistical significance was assessed using 10,000 label permutations with correction for multiple comparisons.

The results showed task related increases and decreases in connectivity across motor, prefrontal, sensorimotor, and cross modal regions. NIRS highlighted slower top-down influences, including prefrontal to motor drive and interhemispheric sensorimotor interactions, while EEG resolved rapid bottom-up dynamics such as motor to prefrontal and visual to somatosensory integration. CMI confirmed that these key connections reflected direct, rather than indirect, interactions.

Together, EEG and NIRS provided complementary perspectives on cortical coordination during MI, yielding convergent but nonredundant evidence for MI specific network organisation. These findings highlight candidate connectivity markers of neuroplasticity with potential relevance for neurofeedback, rehabilitation, and adaptive BCI design.

## Reciprocal connectivity of the auditory thalamus and thalamic reticular nucleus in the guinea pig

**Alexandra O'Brien[1], Kristin Barry[1,2], Helmy Mulders[1]**
[1]Auditory Laboratory, School of Human Sciences, The University of Western Australia | *Crawley, WA 6009, Australia*
[2]Hearing and Balance Research Laboratory, Curtin Medical School, Curtin University | *Bentley, WA 6009, Australia*

Tinnitus is the perception of sound without a corresponding sound stimulus. Tinnitus has been suggested to be the result of dysfunctional thalamocortical signalling, specifically, dysfunctional sensory gating allowing non-salient signalling from the medial geniculate nucleus (MGN) of the thalamus to reach the auditory cortex.

Thalamocortical projections, including projections from the MGN, receive inhibitory input from the thalamic reticular nucleus (TRN). The TRN is a GABAergic structure that regulates multimodal thalamocortical sensory signalling. The auditory subregion of the TRN (aTRN) regulates sensory signalling from the MGN to auditory cortex, and it is potentially a key structure involved in tinnitus. Although the aTRN has been identified in other species, its precise location in guinea pigs is not well described.

Anterograde and retrograde neuroanatomical tracers were iontophoretically injected into the guinea pig MGN. After one week of recovery, animals were transcardially perfused with 4% paraformaldehyde fixative and brain tissue was collected. Brains were then cryoprotected, cut into 50 µm coronal sections and imaged to visualise the tracer-labelled cells and/or fibres with particular interest in the TRN.

Tracer injections in the MGN resulted in labelled fibres and neuronal cell bodies in a ventrocaudal region of the TRN, suggesting this region is reciprocally connected to the MGN and constitutes the aTRN. Labelling in auditory cortex and inferior colliculus confirmed that injections were correctly placed in the MGN. Further studies are underway to investigate non-auditory structures that send projections to the aTRN in a first step to elucidate the circuitry involved in auditory sensory gating.

## Characterisation of inner ear organoids derived from USH2A patient induced pluripotent stem cells

**Joey Lye[1,2], Fiona Leith[1,2], Sharon L Redmond[1,2], Samuel McLenachan[2,3], Fred K Chen[2,3,4], Marcus D Atlas[1,2,5], Elaine YM Wong[1,2,5]**

[1]Ear Science Institute Australia | *Nedlands, WA 6009, Australia*
[2]Centre for Ear Sciences, Medical School, The University of Western Australia | *Nedlands, WA 6009, Australia*
[3]Lions Eye Institute Australia | *Nedlands, WA 6009, Australia*
[4]Royal Perth Hospital | *Perth, WA 6000, Australia*
[5]Curtin Medical School, Curtin University | *Bentley, WA 6102, Australia*

Hearing loss is an irreversible sensory disorder, and it has been estimated to affect over 2.5 billion people worldwide by 2050. Usher syndrome (USH) is the most common autosomal recessive disorder causing both deafness and blindness. USH type 2 (USH2) is the subtype responsible for nearly 50% of USH, and patients are born with moderate-to-severe sensorineural hearing loss. *USH2A* encodes for a large transmembrane protein and is essential for maintaining the stereocilia integrity in developing cochlear hair cells. Mutations are found along the entire *USH2A* gene and there is no available treatment or cure to restore the genetic-associated hearing deficit. In this study, USH2A patient-specific induced pluripotent stem cells (iPSCs) harbouring compound heterozygous *USH2A* c.949C>A and c.1256G>T mutations were used to generate inner ear organoids to model the *USH2A* disease mechanism in the human inner ear. Inner ear organoids containing sensory hair cells were generated through a controlled stepwise differentiation method. We performed immunostaining and gene expression analysis of early otic cell fate markers to examine the effect of *USH2A* mutations during inner ear development. Our results demonstrated that USH2A inner ear organoids were able to form otic vesicles, a sensory epithelium that gives rise to the inner ear during embryogenesis. Furthermore, hair cell and neuronal markers were also expressed in iPSC-derived inner ear organoids, which may provide insights of *USH2A* role at later developmental stages. This preclinical model will be used for high-throughput drug screening and to develop gene therapeutic approaches to correct *USH2A* mutations for hearing restoration.

# SESSION THREE
# Genetics, Metabolism & Molecular Mechanisms in the Brain

## Exploring shared genetic architecture between Alzheimer's Disease and Diabetes-related metabolic biomarkers

**Anika Bushra Lamisa[1,2], Ayeisha Milligan Armstrong[1,2,3], Eleanor K. O'Brien[1,2], Tenielle Porter[1,2,3], Simon M. Laws[1,2,3]**

[1]Centre for Precision Health, Edith Cowan University | *Joondalup, WA 6027, Australia*
[2]Collaborative Genomics & Translation Group, School of Medical & Health Sciences, Edith Cowan University | *Joondalup, WA 6027, Australia*
[3]Curtin Medical School, Curtin University | *Bentley, WA 6102, Australia*

There is strong evidence from epidemiological studies that supports a connection between Alzheimer's Disease (AD) and diabetes. Whilst the precise biological mechanisms remain unclear, there is growing evidence to suggest that diabetes-related metabolic biomarkers may potentially increase AD risk. To explore this link further, this study aimed to comprehensively investigate the genetic relationship between AD and a range of diabetes-related metabolic traits. Genome-Wide Association Study (GWAS) summary statistics were used to explore the shared genetic links between AD and metabolic traits, including glucose, insulin, HbA1c, and adipokines. Linkage disequilibrium score regression (LDSC) and Local Analysis of Co-Variant Association (LAVA) were employed to assess genome-wide and regional genetic correlations, while two-sample Mendelian randomisation (2SMR) evaluated the level of evidence to support potential causal relationships. Gene overlap analyses were also conducted to identify shared genes. LDSC revealed consistent genetic correlations between AD and several metabolic traits: random and 2-hour glucose exhibited nominally significant positive correlations with AD ($rG$ = 0.10–0.22, $p \leq 0.045$), whereas fasting insulin, HbA1c, and proinsulin showed negative correlations ($rG$ = –0.18 to –0.37, $p \leq 0.042$). LAVA identified several genomic loci with significant overlap between AD and multiple metabolic traits. However, 2SMR analyses using the inverse-variance weighted method provided no strong evidence for a causal relationship in either direction. Despite this, gene overlap analyses revealed significant shared genes between AD and these metabolic traits. Overall, these findings highlight notable genetic correlations and shared genes, pointing to potential common biological mechanisms underlying AD and diabetes-related metabolic biomarkers.

## Gene overlap, local genetic correlation, and clinical validation of shared genes between Alzheimer's disease and chronic pain-related disorders

**Olasunkanmi Bamidele[1,2*], Ayeisha Milligan Armstrong[1,3,4,5], Tenielle Porter[1,3,4], Eleanor O'Brien[1,3], Giuseppe Verdile[4,5], ADOPIC Research Consortium, Emmanuel Adewuyi[6], Simon Laws[1,3,4]**

[1]Centre for Precision Health, Edith Cowan University | *Joondalup, WA 6027, Australia*
[2]Faculty of Pharmaceutical Sciences, University of Ilorin | *Ilorin, Kwara 240003, Nigeria*
[3]Collaborative Genomics & Translation Group, School of Medical & Health Sciences, Edith Cowan University | *Joondalup, WA 6027, Australia*
[4]Curtin Medical School, Curtin University | *Bentley, WA 6102, Australia*
[5]Curtin Medical Research Institute, Curtin University | *Bentley, WA 6102, Australia*
[6]Curtin School of Population Health, Curtin University | *Bentley, WA 6102, Australia*

Observational studies suggest an association between Alzheimer's disease (AD) and chronic pain-related disorders (CPDs). Inflammatory mechanisms may underpin this link, but specific pathways remain unclear. Investigating shared genetic architecture may provide valuable insights. Here, publicly available genome-wide association study (GWAS) summary statistics were used to assess the genetic overlap between AD and CPDs, and local genetic correlations using Local Analysis of [co]Variant Association (LAVA). Shared genes were identified using Fisher's Combined P-value (FCP). In a longitudinal cohort, we evaluated these genes against brain health phenotypes, including cognition, brain volumetrics, and brain amyloid-beta (Aβ) burden. Gene overlap analyses revealed significant overlap between genes associated both with AD risk (Jansen 2019) and ankylosing spondylitis ($P = 4.75 \times 10^{-6}$), dorsopathy ($P = 8.55 \times 10^{-4}$), multisite chronic pain (MCP) ($P = 8.55 \times 10^{-8}$), use of NSAIDs ($P = 3.51 \times 10^{-6}$), rheumatoid arthritis ($P = 1.66 \times 10^{-7}$) and osteoarthritis ($P = 6.47 \times 10^{-5}$). The significant overlap between dorsopathy ($P = 3.75 \times 10^{-3}$), MCP ($P = 2.98 \times 10^{-2}$), rheumatoid arthritis ($P = 4.20 \times 10^{-12}$), and AD (Lambert 2013) was also observed in a second study. In addition, LAVA identified loci that contribute disproportionately to genetic correlation at specific loci across the genome. Further analysis of the identified AD-CPD overlapping genes (n = 245) in well-characterised longitudinal cohorts revealed associations between 207 genes and at least one brain-health phenotype investigated ($P<0.05$). Our study suggests shared genetic architecture between AD and CPDs, implicating shared biological mechanisms.

## What we are learning about Alzheimer's disease from genes in the brain's cleaning system

**Ayeisha Milligan Armstrong[1,2,3], Eleanor K. O'Brien[1,2], Shane M. Fernandez[1,2], Vincent Doré[1,4,5], Pierrick Bourgeat[6], Rosita Shishegar[4,7], Paul Maruff[8,9], Christopher C. Rowe[5,8], Victor L. Villemagne[1,5,10], the Alzheimer's Disease Neuroimaging Initiative[*], the AIBL Research Group[^], Tenielle Porter[1,2,3†#], Simon M. Laws[1,2,3†#]**

[1]Centre for Precision Health, Edith Cowan University | Jo*ondalup, WA 6027, Australia*
[2]Collaborative Genomics & Translation Group, School of Medical & Health Sciences, Edith Cowan University | *Joondalup, WA 6027, Australia*
[3]Curtin Medical School, Curtin University | *Bentley, WA 6102, Australia*
[4]Australian E-Health Research Centre, CSIRO | *Parkville, VIC 3052, Australia*
[5]Department of Molecular Imaging & Therapy, Austin Health | *Heidelberg, VIC 3084, Australia*
[6]Australian E-Health Research Centre, CSIRO | *Herston, QLD 4006, Australia*
[7]Department of Electrical & Computer Systems Eng, Monash University | *Clayton, VIC 3800, Australia*
[8]Florey Institute of Neuroscience & Mental Health, The University of Melbourne | *Parkville, VIC 3052, Australia*
[9]Cogstate Ltd | *367 Collins Street, Melbourne, VIC 3000, Australia*
[10]Department of Psychiatry, University of Pittsburgh | *Pittsburgh, PA 15213, USA*

Alzheimer's disease is characterised in part by the accumulation of amyloid-β (Aβ) in the brain. In the healthy brain, a mechanism of Aβ clearance is through the glymphatic pathway, which involves passing through the aquaporin-4 (AQP4) water channel on astrocytic endfeet. Hence, disruptions to glymphatic clearance, for example through the mislocalisation of AQP4, results in reduced Aβ clearance, and increases in both neurodegeneration and cognitive impairment. AQP4 is anchored in place by the dystrophin-associated complex (DAC), with genetic ablation of DAC resulting in AQP4 mislocalisation and Aβ accumulation. Whilst genetic variation in *AQP4* has been previously investigated in AD, variation in the genes that encode for the DAC sub-units has not. For the first time, this study investigated the associations between genetic variation within glymphatic pathway-related genes (*AQP4* and three of the DAC subunit genes) and markers of brain health (brain Aβ burden, cognition and brain volumes). It is likely that the components are interdependent in proper glymphatic pathway functioning, and therefore genetic variants were assessed independently and in combination as a genetic pathway score. Meta-analyses of linear regression results and glymphatic pathway genetic risk score (G-GRS) approaches were undertaken across two independent longitudinal cohorts. At both the individual genetic variant level and polygenic G-GRS level, associations were found with cognition, grey matter and ventricular volumes. These novel findings support a role for genetic variation in glymphatic pathway genes in brain health. They also highlight the utility of biologically informed genetic risk scores in understanding complex disease traits like AD.

## Therapeutic potential of targeting the metabolism pathway in degenerating photoreceptors in mouse models of retinitis pigmentosa

**Kate N. Gilbert[1,2], Alicia A. Brunet[2,3,6], Alan R. Harvey[2,4,5], Livia S. Carvalho[2,3,6]**
[1]School of Biomedical Sciences, The University of Western Australia | *Crawley, WA 6009, Australia*
[2]Lions Eye Institute Ltd. | *Nedlands, WA 6009, Australia*
[3]Centre for Ophthalmology and Visual Sciences, The University of Western Australia | *Crawley, WA 6009, Australia*
[4]Department of Optometry and Vision Sciences, University of Melbourne | *Parkville, VIC, 3052, Australia*
[5]Perron Institute for Neurological & Translational Science | *Nedlands, WA 6009, Australia*
[6]School of Human Sciences, The University of Western Australia | *Crawley, WA 6009, Australia*

Retinitis pigmentosa (RP) is an inherited retinal disease characterised by the primary loss of rod photoreceptors due to a genetic mutation, followed by the secondary loss of cone photoreceptors. While the mechanisms behind this delayed cone death are unclear, changes to cellular metabolism have been implicated. Investigation into therapies that target the metabolism pathway show potential benefits for photoreceptors in RP, though further research is required. In this study, we used the retinal degeneration 1 (*rd1*) mouse model of autosomal recessive RP and the *Rho*$^{P23H/WT}$ mouse model of autosomal dominant RP to characterise the metabolites associated with aerobic glycolysis and oxidative phosphorylation (OXPHOS) using metabolomic analysis. Previous studies have suggested a metabolic shift from aerobic glycolysis to OXPHOS in RP-affected cones, thus we expect to see increased OXPHOS-related metabolites in both disease models compared to healthy controls. To evaluate if targeting metabolic pathways could have therapeutic effects in our RP models, we tested a single dose of two metabolism-modulating drugs: SC79 and GSK-J4. Our results show that there was a trend for increased retinal thickness in the *rd1* mouse after treatment with SC79. However, the sham injected group showed reduced retinal thickness, indicating the injections themselves may have limited the neuroprotective effects of SC79. In contrast, GSK-J4 treated animals showed minimal therapeutic effects in either RP model. Analysis is ongoing in order to determine whether the metabolism pathway is indeed a potential therapeutic target for RP.

## Evaluating the effect of histone deacetylase inhibition in the *Cnga3*$^{-/-}$ mouse model of achromatopsia

**Miya Sandesh[1,2], Alicia A. Brunet[2,3,4], Annie L. Miller[2,3], Livia S. Carvalho[2,3,4]**
[1]School of Biomedical Sciences, The University of Western Australia | *Crawley, WA 6009, Australia*
[2]Lions Eye Institute | *Nedlands, WA 6009, Australia*
[3]Centre for Ophthalmology & Visual Sciences, The University of Western Australia | *Crawley, WA 6009, Australia*
[4]Department of Optometry & Vision Sciences, University of Melbourne | *Parkville, VIC 3052, Australia*

Achromatopsia is a type of inherited retinal disease that results in the dysfunction or degeneration of cone photoreceptors, affecting one in 30,000 people. Currently, no curative treatment exists, and the primary mechanisms of cone death remain unknown. One hypothesis is that histone deacetylase (HDAC) overactivity may cause cone death, with one study showing that HDAC activity peaked at P35. The current study aims to determine whether administration of the FDA-approved pan HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) either later in disease progression (P60), around or shortly after the peak of HDAC overexpression (P30, P35, P40), can prevent cone loss. After an intravitreal injection of either SAHA or a sham control at P30, P35, P40, or P60 in *Cnga3*$^{-/-}$ mice, the eyes were collected four days post-treatment for histological analysis. Cone numbers were quantified from central (superior and inferior) and peripheral (superior and inferior) retinal areas. The first group analysed were treated around P40 and eyes were collected four days post-injection. After treatment with SAHA, there was no significant difference in cone numbers ($P$=0.6923, two-way ANOVA with Tukey's post hoc, n=6). The analysis of the remaining groups is still underway, with HDAC inhibition showing no protective effects thus far but we hypothesise that treatment may be beneficial when injected slightly before or at the peak of HDAC overactivity (P35).

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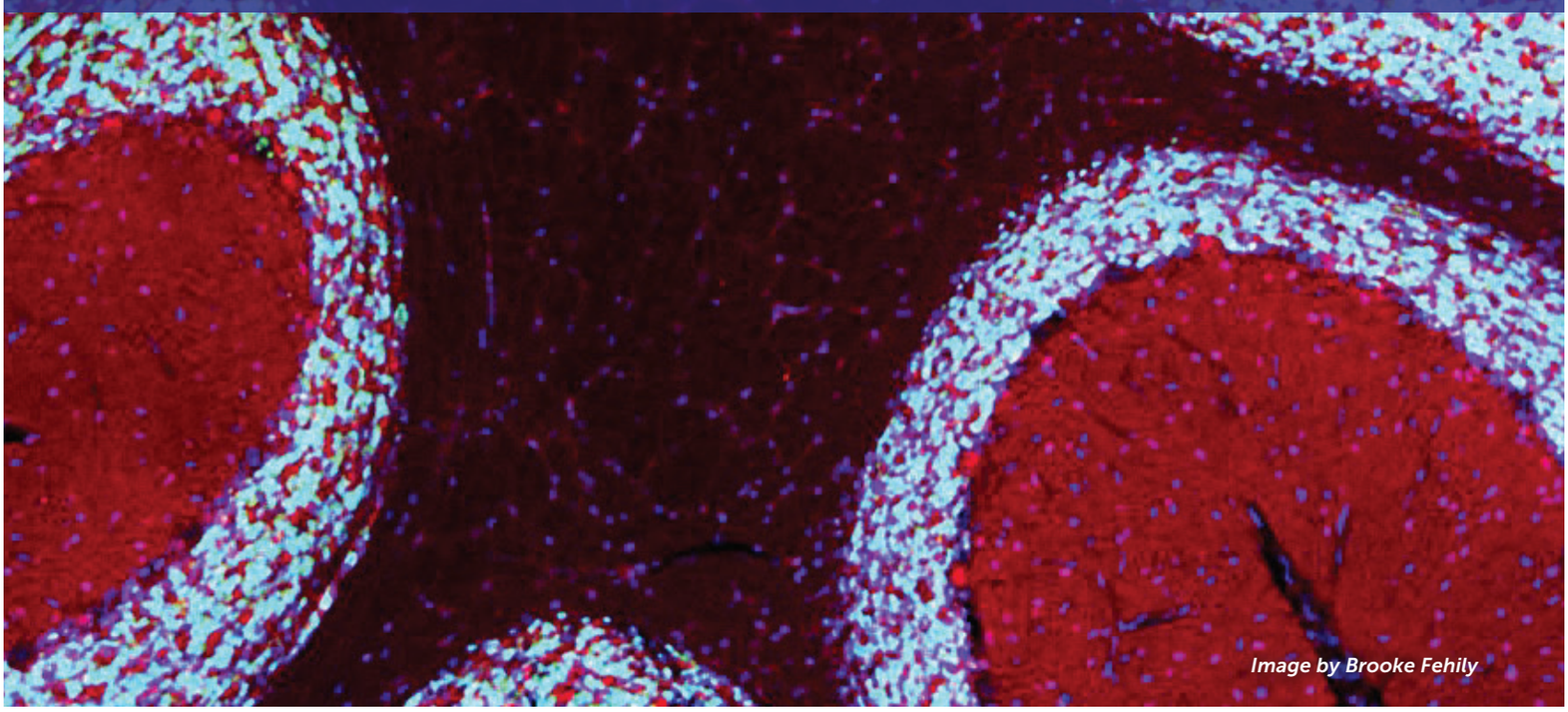

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# SESSION FOUR
## BEHAVIOUR, PERCEPTION & OUTCOMES IN BRAIN DISORDERS

### Predicting recovery outcomes following mild traumatic brain injury in an Australian community-based population: results from the Concussion Recovery Study (CREST)

**JACINTA THORNE[1,2,3], JEMMA KEEVES[1,2], ALEKSANDRA K. GOZT[2,4], SARAH C. HELLEWELL[1,2], GILL COWEN[1,5,6], ELIZABETH THOMAS[7,8], ALEXANDER RING[3,9], HUIJUN CHIH[6], CAERWEN BEATON[1,2], FRANCESCA BUHAGIAR[10], AMANDA JEFFERSON[5], MELISSA PAPINI[1,2], GLENN ARENDTS[11,12], ANTONIO CELENZA[11,13], BEN SMEDLEY[12,14], SJINENE VAN SCHALKWYK[15], JOHN CHARLES ILIFF[5,16,17,18,27], NICOLE GHEDINA[19], RUSSELL YOUNG[20], MONICA MARTON[21], SUZANNE ROBINSON[1,22], MELISSA LICARI[23], DAN XU[5,6,24], STEPHEN HONEYBUL[25], MICHAEL BYNEVELT[26], CARMELA PESTELL[10], DANIEL FATOVICH[27,28] AND MELINDA FITZGERALD[1,2,4]**

[1]Curtin Medical Research Institute, Curtin University | *Bentley, WA 6102, Australia*
[2]Perron Institute for Neurological & Translational Science | *Nedlands, WA 6009, Australia*
[3]Curtin School of Allied Health, Faculty of Health Sciences, Curtin University | *Bentley, WA 6102, Australia*
[4]Connectivity Traumatic Brain Injury Australia | *Nedlands, WA 6009, Australia*
[5]Curtin Medical School, Faculty of Health Sciences, Curtin University | *Bentley WA 6102, Australia*
[6]School of Population Health, Curtin University | *Bentley WA 6102, Australia*
[7]Centre for Clinical Research Excellence, School of Population Health, Curtin University | *Bentley WA 6102, Australia*
[8]School of Medicine, The University of Western Australia | *Nedlands, WA 6009, Australia*
[9]Institute for Immunology & Infectious Diseases, Murdoch University | *Murdoch, WA 6150, Australia*
[10]School of Psychological Science, The University of Western Australia | *Nedlands, WA 6009, Australia*
[11]Discipline of Emergency Medicine, School of Medicine, The University of Western Australia | *Nedlands, WA 6009, Australia*
[12]Emergency Department, Fiona Stanley Hospital | *Murdoch, WA 6150, Australia*
[13]Emergency Department, Sir Charles Gairdner Hospital | *Nedlands, WA 6009, Australia*
[14]Emergency Department, Rockingham General Hospital | *Rockingham, WA 6168, Australia*
[15]Emergency Department, Joondalup Health Campus | *Joondalup, WA 6027, Australia*
[16]Emergency Department, St John of God Hospital | *Murdoch, WA 6150, Australia*
[17]School of Medicine, The University of Notre Dame | *Fremantle, WA 6160, Australia*
[18]Royal Flying Doctor Service - Western Operations | *Perth, WA 6105, Australia*
[19]Emergency Department, St John of God Midland Public Hospital | *Midland, WA 6056, Australia*
[20]Emergency Department, Albany Regional Hospital | *Albany, WA 6330, Australia*
[21]Emergency Department, Geraldton Regional Hospital | *Geraldton, WA 6530, Australia*
[22]Deakin Health Economics, Institute for Health Transformation, School of Health & Development, Deakin University | *Burwood, VIC 3125, Australia*
[23]The Kids Research Institute Australia | *Crawley, WA, 6009 Australia*
[24]The First Affiliated Hospital, Sun Yat-Sen University | *Guangzhou, Guangdong 510080, China*
[25]Statewide Director of Neurosurgery, Department of Health, Government of Western Australia | *Perth, WA 6000, Australia*
[26]The Neurological Intervention & Imaging Service of Western Australia, Sir Charles Gairdner Hospital | *Nedlands, WA 6009, Australia*
[27]Emergency Medicine, Royal Perth Hospital | *Perth, WA 6000, Australia*
[28]Centre for Clinical Research in Emergency Medicine, Harry Perkins Institute of Medical Research | *Nedlands, WA 6009, Australia*

Most people recover well following mild traumatic brain injury (mTBI), however some experience persisting post-concussion symptoms (PPCS). Our aims were (i) to evaluate the presence and impact of PPCS on return to work, sport and study over a 12-month period; and (ii) to identify factors that may predict people at risk of PPCS in an Australian community-based cohort.

Prospective, longitudinal cohort study of adults (18-65 years) with recent mTBI (<7 days). Demographic characteristics, pre- and peri-injury factors, and acute concussion symptoms (Post-Concussion Symptom Scale (PCSS)) were collected via telephone. Primary outcome: PCSS symptom severity score >6 males; >7 females. Predictive factors for PPCS at 3- and 12- months were identified from logistic regression modelling.

232 participants (median 33yrs, 101(43.5%) female, 74(31.9%) sports-related mTBI). At 3-months post-injury, 82/165(49.7%) reported PPCS. Of those working pre-injury, 96.7% had returned to work by 3-months, with nearly 50% of people working experiencing PPCS. Univariate analyses revealed that prior mental health issues, prescription medication use, previous regular exercise and mechanism of injury were associated with PPCS; but loss of consciousness, retrograde, and post-traumatic amnesia were not. Participants with 'high' initial PCSS Scores (>=30) were six times more likely to experience PPCS at 3-months (aOR=6.17, 95%CI =2.63-14.46, p<0.001, pseudo-$R^2$=0.281), and almost three times as likely to have PPCS at 12-months (aOR=2.73, 95%CI= 1.05-7.12, p=0.039, pseudo-$R^2$=0.305).

Of those participants who completed follow-up, almost half reported experiencing persisting symptoms at three months. Nearly half of participants continued to work while symptomatic. High PCSS scores may assist clinicians to identify people at risk of persisting symptoms following mTBI, ensuring timely healthcare follow-up for those with greatest need.

## Characterising the appearance and perceived severity of visual snow

**Cassandra J Brooks[1,2], Yu Man Chan[2], Joanne Fielding[3], Owen B White[3], David R Badcock[4], Allison M McKendrick[1,2]**

[1]Lions Eye Institute & School of Health and Clinical Sciences, The University of Western Australia | *Nedlands, WA 6009, Australia*
[2]Department of Optometry and Vision Sciences, University of Melbourne | *Parkville, VIC 3052, Australia*
[3]Department of Neurosciences, Central Clinical School, Monash University | *Clayton, VIC 3800, Australia*
[4]School of Psychological Science, The University of Western Australia | *Crawley, WA 6009, Australia*

Visual snow syndrome is a poorly understood neurological condition that affects visual quality of life. The defining symptom is visual snow, a continuous visual disturbance resembling television static. To improve characterisation of this symptom, we aimed to quantify visual snow appearance and explore patient perceptions of the effects of visual snow on daily visual experience.

23 participants with visual snow syndrome separately estimated their visual snow dot size, density, brightness and flicker speed by matching to an external simulation. Participants reported the severity of their visual snow, separately rating perceived visibility, interference with vision, effort to ignore and level of annoyance on an 11-point numerical scale.

Mean and 95% confidence intervals for visual snow appearance were: size (6.0, 5.8 - 6.3 arcseconds), separation (2.0, 1.7 - 2.3 arcmin), luminance (72.4, 58.1 - 86.8 cd/m$^2$) and flicker rate (25.8, 18.9 – 32.8 frames per image at 120 Hz). The perceived visibility of visual snow was linked to its measured density, as finer dot spacing was associated with higher visibility ratings ($\tau_b$=−0.41, $p$=0.01). The self-rated visibility of visual snow was also positively correlated with the perceived interference with vision ($\tau_b$=0.36, $p$=0.04) and effort to ignore ($\tau_b$=0.48, $p$=0.005).

We have successfully developed a method for quantifying visual snow appearance that may be useful in stratifying patients and evaluating potential treatments in clinical trials. Understanding the fine spatial scale of visual snow provides clues to its likely neural basis and will assist the development of targeted tests of the effects of visual snow on vision.

## No difference in muscle coactivation during submaximal plantarflexion contractions in individuals with Multiple Sclerosis compared to matched controls

**Kym Wansbrough[1], Janet L. Taylor[1], Matheus D. Pinto[2], Tony Blazevich[2], Travis Cruickshank[1], Lars Hvid[3], Christopher Latella[1]**

[1]Centre for Precision Health, Edith Cowan University | *Joondalup, WA 6027, Australia*
[2]School of Medical and Health Sciences, Edith Cowan University | *Joondalup, WA 6027, Australia*
[3]Department of Public Health, Aarhus University, Denmark | *Aarhus, 8000, Denmark*

While fatigue and motor dysfunction in Multiple Sclerosis (MS) is well-documented, the specific patterns of muscle activity during controlled submaximal tasks are not fully understood.

We compared muscle activity between individuals with MS (n=14, 10 female, age 44.9±15.0 years, median Patient Determined Disease Steps (PDDS)=3 [a disability scale out of 8]) and healthy age-matched controls (n=13, 9 female, age 46.6±14.9 years). Participants completed the Fatigue Severity Scale (FSS), then performed 20-second isometric ramp voluntary plantar flexor contractions at 10%, 20%, and 30% of maximum. Surface electromyography recorded antagonist muscle activation from tibialis anterior during contraction.

Mann-Whitney U tests revealed that MS participants (42.71±13.38 [mean and SD]) demonstrated significantly greater fatigue on the FSS than healthy controls (23.85±7.01), p<0.001, r=0.808 (large effect). Antagonist coactivation was not different to healthy controls during contractions at 20% (p=0.165) and (30% p=0.149) although a non-significant, but moderate effect at 10% (p=0.053, r=0.462) was observed.

Given no difference in coactivation, other changes in neuromuscular drive or motor control of agonist muscle(s) may be responsible for poorer motor function, and reported fatigue and muscle weakness common to MS. However, such claims require further investigation.

## An observational Study of Head Injury Assessments and Mechanisms of Head Impact in Australian National Rugby League

**REECE GRANGER**[1,2,3], **SARAH HELLEWELL**[2,3]
[1]School of Biomedical Sciences, The University of Western Australia | *Crawley, WA 6009, Australia*
[2]Perron Institute for Neurological & Translational Science | *Crawley, WA 6009, Australia*
[3]Curtin Medical Research Institute | *Bentley, WA 6102, Australia*

Sports-related concussion, a mild traumatic brain injury, is common in contact sports such as the Australian National Rugby League (NRL). To enhance detection and player safety, the NRL introduced Head Injury Assessment (HIA) protocols, though limited observational data has been publicly available since 2020. This study examined the incidence and characteristics of HIAs and concussions across the 2024 NRL season, focusing on playing positions, injury mechanisms, physician involvement, and return-to-play timelines.

A retrospective analysis was conducted across 204 matches in the 2024 home-and-away season. Match records, official injury lists and video reviews were used to identify HIA events and concussion diagnoses. Proportional and descriptive statistics were applied to evaluate incidence rates and positional patterns.

Across the 2024 season, 246 HIAs were recorded (34.87 per 1,000 player-match hours), with 95 confirmed concussions (13.46 per 1,000 player-match hours); approximately one every two matches. Forwards received the majority of HIAs (62.2%), while outside backs demonstrated higher concussion rates per HIA, exceeding 55% in some positions. The leading mechanisms of injury were tackler-to–ball carrier contact (35.8%) and head-to-head collisions (18.9%). Independent doctors issued 110 HIAs with a 50% failure rate, compared with 25.6% failure among club doctors. Average return-to-play was 14.35 days.

Concussion incidence in 2024 remained consistent with historical ranges but reflected evolving mechanisms and positional risk, shaped by recent rule changes and protocols. Findings highlight the importance of continued surveillance, refinement of tackling regulations and need to address reporting mechanisms to strengthen athlete welfare in professional rugby league.

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# SESSION FIVE

# CANCER, METABOLIC HEALTH & COGNITION

## Effects of eccentric versus stretching exercise training on cognitive function of older women

**KEN NOSAKA[1], MIN-JYUE HUANG[1]**
[1]School of Medical & Health Sciences, Edith Cowan University | *Joondalup, WA 6027, Australia*

Exercises focusing on eccentric contractions may stimulate the brain better, improving cognitive function. We tested the hypothesis that executive function and attention would improve more after eccentric resistance exercise (ECC) than stretching exercise (STRETCH) training. Healthy older women (65–75 years) underwent either ECC ($n$=14) or STRETCH ($n$=14) intervention for 8 weeks. ECC consisted of seven exercises emphasising eccentric contractions while STRETCH performed 12 stretching exercises, with supervised sessions undertaken twice weekly accompanied by a home-based program. Executive function and attention were assessed using the Stroop test of color naming (STCN) and conflicting color words, symbol digit modalities test, digit span test (DST), and trail making tests (TMT-A and TMT-B), and six physical function tests were undertaken before and after the 8-week training period. Fasting blood samples were obtained before and after the training. A significant ($p$<0.05) group×time interaction effect was evident for STCN, DST, and TMT-A, with only ECC showing improvements (DST:14.7±27.0% and TMT-A:10.2±12.0%) from pre- to post-training. No significant changes in other cognitive function tests were found for either group. All physical function tests except one-leg balance test showed greater improvement ($p$<0.05) for ECC than STRETCH. No significant changes in blood lipid profile and brain-derived neurotrophic factor were found, but serum glucose concentration and glycosylated hemoglobin decreased ($p$<0.05) in ECC. These results suggest that a short-term body-weight eccentric exercise intervention was effective in enhancing components of cognitive and physical function of older women and may prove a useful strategy in combatting age-related decline in cognitive and physical function.

## Late Effects of Radiation in a Juvenile Preclinical Model of Paediatric Brain Cancer

**HELENA BERTAZZO[1,2], ANNABEL SHORT[2], JAMIE BEROS[1], CHRIS BUTLER[2], ALEXANDRA MONSON[2], JESSICA BUCK[2], AIDEN BOONNARK[1,2], JENNIFER RODGER[1], RAELENE ENDERSBY[2]**
[1]School of Human Sciences, the University of Western Australia | *Crawley, WA 6009, Australia*
[2]Brain Tumour Research Group, The Kids Research Institute | *Crawley, WA 6009, Australia*

Brain cancer in children disrupts critical development, and its harsh treatments lead to long term side effects greatly diminishing quality of life in adulthood. Radiotherapy is associated with neurocognitive deficits, and disrupts cellular processes, leading to late effects prevalent years after treatment. However, preclinical testing does not routinely assess treatments for late effects. We hypothesised that structural and functional changes post-radiotherapy in our pre-clinical model would mimic those in children, allowing future treatments to be tested for late effects. We further hypothesised that increased synaptic density drives cortical expansion seen after fractionated radiotherapy, possible contributing to tissue sparing. Juvenile mice were treated at postnatal day (P) 16 with either a single dose of 8 Gy whole-brain irradiation or a mathematically equivalent fractionated dose of 18 Gy (9 × 2 Gy daily fractions). Control mice received either a single or 9x cone-beam computed tomography (CBCT) scans. At P63, mice underwent a behavioural battery associated with brain areas demonstrating volume changes after radiotherapy, assessing cognition, olfaction and social behaviours. Brains were harvested for Golgi staining to investigate dendritic spines as a marker of synaptic density, and for immunofluorescence synaptic staining. Fractionated radiotherapy during early life induced neurocognitive deficits in mice akin to those observed in patients. Radiotherapy generated impairments on a hippocampal-dependent spatial memory task and preliminary data demonstrates effects radiation and dosing schedule on sociability. As behavioural effects in this model are akin to those in paediatric brain cancer survivors, this model shows promise to screen for late effects.

## Blood-based biomarkers for the detection of melanoma brain metastasis

**Désirée Sexauer[1,2*], Russell J Diefenbach[3,4*], Lydia Warburton[1,2,5], Ashleigh Stewart[3,4], Anna L Reid[1,2], Wei Yen Chan[3,4], Jenny H Lee3,4, Alexander M Menzies[4,6,7], Inês Pires da Silva[4,7,8], Georgina V Long [4,6,7], Pauline Zaenker[1,2], Aaron B Beasley[1,2], Elin S Gray[1,2†], Helen Rizos[3,4†]**

[1]Centre for Precision Health, Edith Cowan University | *Joondalup, WA 6027, Australia*
[2]School of Medical & Health Sciences, Edith Cowan University | *Joondalup, WA 6027, Australia*
[3]Faculty of Medicine, Health & Human Sciences, Macquarie University | *Macquarie Park, NSW 2109, Australia*
[4]Melanoma Institute Australia | *Sydney, NSW 2065, Australia*
[5]Department of Medical Oncology, Fiona Stanley Hospital | *Murdoch, WA 6150, Australia*
[6]Department of Medical Oncology, Royal North Shore Hospital and Mater Hospitals | *Sydney, NSW 2065, Australia*
[7]Faculty of Medicine and Health, The University of Sydney | *Sydney, NSW 2006, Australia*
[8]Charles Perkins Centre, University of Sydney | *Camperdown, NSW 2050, Australia*
*Shared co-first authorship | † Shared co-senior authorship

Brain metastases in melanoma are typically diagnosed following neurological symptoms or imaging, often at advanced stages. Early detection of asymptomatic brain metastases is crucial, as progression can lead to severe neurological decline, diminished quality of life, and death.

This study examined circulating biomarkers, including microRNAs, tumour-associated autoantibodies, and brain-derived cell-free DNA (cfDNA) methylation— from baseline blood samples of melanoma patients with intracranial metastases and those with extracranial-only metastases. For cfDNA methylation analysis, 47 patients with brain metastases and 97 with extracranial only metastases were included. The microRNA cohort consisted of 125 patients. Autoantibody profiling was conducted on 95 serum samples. MicroRNA libraries were sequenced on the Ion Torrent S5 Prime. Differential expression analysis was conducted using *edgeR*, with significance defined as a fold change ≥1.2 and a false discovery rate (FDR) ≤ 0.001. Validation with TaqMan MicroRNA Assays is planned. Autoantibody biomarkers were identified using HuProts v.4 (~17,000 proteins); IgG markers will be validated on custom arrays. cfDNA methylation was analysed using a custom QIAseq Targeted Methyl Panel of brain-specific CpGs; a refined panel will be developed for validation.

One microRNA (microRNA-1246) was significantly enriched in patients with brain metastases (log2FC = 1.99, FDR = 0.000021). 49 IgG autoantibodies ($p<0.01$, log2FC>1.5, AUC ≥ 0.7) were elevated in the brain metastasis group. Eight cfDNA methylation markers also showed promise (FDR< 0.05).

A multi-analyte approach using circulating biomarkers may enable earlier, non-invasive detection of brain metastases in melanoma. A validation cohort is currently under evaluation.

## Changes in fasting plasma insulin, fasting plasma glucose and insulin resistance are associated with longitudinal cognitive function

**Amy Woodfield[1,2], Tenielle Porter[1,3,4], David Groth[1,2], Simon M. Laws[1,3,4], Giuseppe Verdile[1,2,5] & The AIBL Research Group**

[1]Curtin Medical School, Curtin University | *Bentley, WA 6102, Australia*
[2]Curtin Medical Research Institute, Curtin University | *Bentley, WA 6102, Australia*
[3]Centre for Precision Health, School of Health & Medical Sciences, Edith Cowan University | *Joondalup, WA 6027, Australia*
[4]Collaborative Genomics & Translation Group, School of Health & Medical Sciences, Edith Cowan University | *Joondalup, WA 6027, Australia*
[5]School of Health & Medical Sciences, Edith Cowan University | *Joondalup, WA 6027, Australia*

Insulin resistance is associated with cognitive impairment and may contribute as an underlying pathomechanism for Alzheimer's Disease (AD). Where insulin resistance has the greatest impact on AD progression remains unclear. Our previous analyses in AIBL reported cross-sectional associations between insulin resistance, cognition, and AD biomarkers. Longitudinally, this study explores the relationship between insulin resistance (HOMA-IR), fasting plasma insulin (FPI), fasting plasma glucose (FPG) and cognitive function.

Linear mixed modelling was used to assess baseline FPI, FPG or HOMA-IR act as predictors for cognitive change, and linear regression analyses to test longitudinal associations between FPI, FPG or HOMA-IR and cognition. Sex and brain amyloid-β (Aβ) burden were also explored.

Baseline FPI, FPG and HOMA-IR were not independent predictors for cognitive change, though associations were observed following stratification by sex and brain Aβ burden. Lower baseline FPI was associated with executive function decline in males, and the decline of visual recognition and language in those with brain Aβ burden. High brain Aβ burden and increasing FPG were associated with verbal episodic, visual recognition and global cognition decline. Lastly, increasing FPI or HOMA-IR was associated with visual recognition decline and an increase in FPG associated with executive function decline.

Our findings suggest that baseline FPI, FPG or HOMA-IR alone are not associated with cognitive change. Rather, relationships are only observed when assessing change over time. This provides an insight into the relationship between measures of glucose homeostasis and specific cognitive decline and may have implications for interventions targeting these measures in neurodegenerative disease.

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# POSTER ABSTRACTS

## Targeting stress in Alzheimer's disease: Evaluating mineralocorticoid receptor modulators and gene variants on microglial function

**Amy O'Keeffe[1], Marnie Petrucci[1], Ayeisha Milligan-Armstrong[1], David Groth[1], Giuseppe Verdile[1,2]**
[1]Curtin Medical School & Curtin Medical Research Institute, Faculty of Health Sciences, Curtin University | *Bentley, WA 6102, Australia*
[2]School of Medical & Health Sciences, Edith Cowan University | *Joondalup, WA 6027, Australia*

Chronic stress has been associated with promoting neurodegenerative diseases through dysregulating the Hypothalamic-Pituitary-Adrenal (HPA) axis and increasing cortisol levels. High cortisol levels have been observed in Alzheimer's disease (AD) patients and promotes the progression of AD pathology. The cellular action of cortisol is mediated by the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR), with MR being involved in setting the HPA-axis activation threshold. In addition, studies have revealed the importance of the MR in neuronal cells. However, little is known about its role in microglia which are thought to become maladaptive in AD. Thus, the project aims to assess the impact of modulating MR in microglia. Human microglia cell-line (HMC3) were treated with MR agonist, Fludrocortisone, or MR antagonist, Spironolactone and gene expression was assessed through RNA sequencing. These molecules led to differential expression of several genes, including some related to stress responses, neuroinflammation, and AD. To confirm a major role for the MR in microglia function, current work is assessing the effects of combing MR and GR modulators, as well as establishing HMC3 models of MR KO. The next steps are to express and evaluate the effect of MR haplotypes that are known to alter MR activation and assess their impacts on microglial function via morphology, phagocytosis, migration, and cytokine production analyses. Overall, the findings from this study will provide novel insights into the role of the MR in microglial function and have implications in targeting this receptor in neurodegenerative diseases.

## HA1 (a Probucol Analogue) Lowers Aβ Level and Prevents Blood-Brain Barrier Dysfunction in Diabetic Mice

**Arazu Sharif [1,2,3], John Mamo [1,2,3], Virginie Lam [1,2,3], Ryu Takechi [1,2,3]**
[1]Curtin Medical Research Institute, Faculty of Health Sciences, Curtin University | *Bentley, WA 6102, Australia*
[2]Perron Institute for Neurological and Translational Research | *Nedlands, WA 6009, Australia*
[3]School of Public Health, Faculty of Health Sciences, Curtin University | *Bentley, WA 6102, Australia*

Heightened vascular exposure to elevated levels of lipoprotein-Aβ and free Aβ contributes to blood–brain barrier (BBB) dysfunction and the onset of neurodegenerative processes. Disturbances in lipoprotein metabolism can exacerbate this exposure by increasing lipoprotein-Aβ production in lipogenic organs, such as the intestine, and reducing its clearance from circulation. In diabetes, BBB disruption may therefore arise from enhanced capillary exposure to lipoprotein-Aβ driven by metabolic imbalance.

Probucol, a historic lipid-lowering agent, has previously been shown to suppress intestinal lipoprotein-Aβ production and secretion, thereby protecting against diet-induced BBB dysfunction in murine models. However, its high hydrophobicity limits bioavailability and therapeutic utility. To overcome this, our laboratory has developed a novel probucol analogue. In this study, we used the db/db mouse model of diabetes to test whether probucol and its analogue, through modulation of peripheral lipoprotein-Aβ, preserve BBB integrity and prevent neurovascular inflammation.

In control db/db mice, the results indicated elevated enterocytic Aβ, increased plasma Aβ42 and Aβ oligomer levels, and heightened BBB permeability. Both probucol and equimolar doses of the analogue reduced intestinal Aβ production. Notably, only the probucol analogue lowered circulating Aβ42 and Aβ oligomer levels and prevented BBB dysfunction, oxidative stress, and neuroinflammation.

Together, these findings highlight the therapeutic potential of the novel probucol analogue in modulating peripheral Aβ metabolism and protecting BBB function in diabetes.

## Assessing the efficacy of neurofeedback to restore brain volume after mild traumatic brain injury

**Blake Rippon[1,2,3], Amanda Jefferson[1,2,3], Sarah Hellewell[1,2,3,4]**
[1]Curtin Medical Research Institute, Curtin University | *Bentley, WA 6102, Australia*
[2]The Perron Institute for Neurological & Translational Science | *Nedlands, WA 6009, Australia*
[3]Curtin Medical School, Curtin University | *Bentley, WA 6102, Australia*
[4]Centre for Neuromuscular & Neurological Disorders, University of Western Australia | *Crawley, WA 6009, Australia*

Mild traumatic brain injury (mTBI) is a rapid mechanical impact to the head that can result in debilitating symptoms. Up to 50% of people with mTBI experience symptoms extending 3 months post-injury, termed persistent post-concussive symptoms (PPCS). Treatment options for PPCS are limited, often targeting individual symptoms. Neurofeedback, a non-invasive method to alter brain function, has shown optimistic report in reducing symptoms in several neurological conditions, though its biological effects are unknown. The efficacy of neurofeedback can be assessed via magnetic resonance imaging (MRI), detecting subtle gray matter volume (GMV) changes.

This study investigates neurofeedback's impact on cognition, symptom burden, quality of life (QoL) and GMV in individuals with PPCS (6 months – 4 years post-injury; n = 41). Participants were randomised into one of three groups: neurofeedback, nondirected training or control. All underwent pre- and post-intervention, T1-weighted 3T MRI scans, alongside assessments for symptom burden (Post Concussion Symptom Scale), QoL (reported as an after-brain injury outcome score) and cognition (standardised tests). Quantitative electroencephalography identified dysfunctional brain regions and frequencies to develop personalised neurofeedback protocols. MRI scans were analysed using FreeSurfer to quantify GMV and cortical thickness.

We hypothesise the neurofeedback group will demonstrate significant improvements in symptom resolution, cognitive function and QoL, along with improved GMV and thickness compared to the other groups. This ongoing randomised controlled study aims to develop our understanding of the structural changes in PPCS and identify neurofeedback's effect on brain plasticity. If effective, neurofeedback could be implemented as a reliable therapeutic strategy for PPCS.

## Development of Usher syndrome 1B patient-derived inner ear organoid model

**Fiona Leith[1,2], Joey Lye[1,2], Sharon L Redmond[1], Samuel McLenachan[2,3], Fred K Chen[2,3,4], Marcus D Atlas[1,2,5], Elaine YM Wong[1,2,5]**
[1]Ear Science Institute Australia | *Nedlands, WA 6009, Australia*
[2]Centre for Ear Sciences, Medical School, The University of Western Australia | *Nedlands, WA 6009, Australia*
[3]Lions Eye Institute Australia | *Nedlands, WA 6009, Australia*
[4]Royal Perth Hospital | *Perth, WA 6000, Australia*
[5]Curtin Medical School, Curtin University | *Bentley, WA 6102, Australia*

MYO7A mutations are one of the top 20 causes of genetic deafness, resulting in autosomal dominant (DFNA11), autosomal recessive (DFNB2) hearing loss and a subtype of Usher Syndrome, the leading cause of deaf-blindness. Patient-derived induced pluripotent stem cell (iPSC) models of genetic diseases have the advantage of reflecting the complexities of the human genetic background that can affect disease presentation. Especially in diseases with mutation in genes for proteins involved in complex interactions such as Usher syndrome. This project aims to generated, characterise and differentiate patient-derived iPSCs with homozygous c.496del MYO7A mutations into inner ear organoids that reflect genetic and structural effects of Usher on critical inner ear sensory cells. The iPSC will be characterised for pluripotency by flow cytometry, PCR gene expression analysis and immunohistochemistry. Morphology is assessed daily by brightfield microscopy. The MYO7A mutation site will be sequenced to ensure the mutation was maintained. The iPSC are differentiated to inner ear organoids via timed modification of the FGF, TGFβ, BMP and Wnt signalling pathways to direct cells down the otic fate pathway from non-neural ectoderm to sensory epithelia. The patient-derived iPSCs maintained the c.496del mutations and expressed pluripotency markers indicative of a stem cell state. Organoids at day 70 of differentiation via the Ear Science patented protocol have been grown and will undergo further culture to increase maturity and examination for otic development markers and inner ear cell types. These organoids will be used as a patient-specific disease model for a prime editing CRISPR based therapy.

## Assessing the effect of accelerated rTMS on synaptic plasticity in a mouse model of depression

**Kamolchanok Panichsakul[1,3], Alex Tang[2,3], Jamie Beros[1,3]**
[1]School of Human Sciences, The University of Western Australia | *Crawley, WA 6009, Australia*
[2]School of Biomedical Sciences | *Crawley, WA 6009, Australia*
[3]Perron Institute for Neurological & Translation Science | *Nedlands, WA 6009, Australia*

Major Depressive Disorder (MDD) is a leading cause of disability worldwide with an increasing prevalence since the COVID-19 pandemic. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive intervention for treatment-resistant depression used to promote various forms of neuroplasticity such as synaptic plasticity. Recently, accelerated rTMS protocols—delivering multiple stimulation sessions within a single day—have gained attention for their potential to shorten treatment courses and enhance outcomes. However, the neurobiological mechanisms underlying accelerated rTMS remain unclear.

This study investigated whether accelerated rTMS enhances synaptic plasticity in a mouse model of depression. A depression-like phenotype was induced by chronic corticosterone (CORT) supplementation via drinking water (100μM) for 3 weeks. This well-established paradigm mimics prolonged stress exposure and can induce depression-like changes and maladaptive neuroplasticity. To examine synaptic plasticity, Thy1-YFP transgenic mouse line were used, in which a subset of cortical neurons expresses yellow fluorescent protein. This enables visualization and quantification of dendritic spines, a key marker of synaptic plasticity. Following CORT exposure, animals were assigned to either active intermittent theta burst stimulation (iTBS, 192 sec, 1800 pulses, 120mT) or time matched sham stimulation targeted to the prefrontal cortex. Stimulation was delivered three times daily with 15-minute rest intervals between stimulation sessions for 10 days. After the stimulation period, brains were collected for post-mortem imaging to assess dendritic spine density. Imaging and data analysis is currently ongoing, however we expect the findings are going to reveal whether accelerated rTMS enhances dendritic spine plasticity and supports its use as a rapid, effective treatment for MDD.

## Bridging Gaps in Functional Neurological Disorder: Developing a Dance and Movement Therapy Program through Co-design

**Sneha Rajagopalan[1,2], Penelope Blanco Ochoa[2,6], Alexandra Fisher[4], Lay Kun Kho[5], Christopher Latella[1,2], Travis Cruickshank[1,2,3]**
[1]Centre for Precision Health, Edith Cowan University | *Joondalup, WA 6027, Australia*
[2]School of Medical and Health Sciences, Edith Cowan University | *Joondalup, WA 6027, Australia*
[3]Perron Institute for Neurological & Translation Research | *Nedlands, WA 6009, Australia*
[4]Birmingham & Solihull Mental Health Foundation Trust, University of Birmingham | *Edgbaston, Birmingham B15 2TT, United Kingdom*
[5]Royal Perth Hospital, Victoria Square | *Perth, WA 6000, Australia*
[6]Western Australia Academy of Performing Arts | *Mount Lawley, WA 6050, Australia*

Dance and Movement Therapy (DMT) is an embodied intervention that has been documented to positively impact people living with a range of neurodegenerative disorders such as Parkinson's disease and multiple sclerosis. Specifically, improvements have been demonstrated in physical and quality of life measures within these populations. Evidence for the use of DMT in neurodegenerative disorders are steadily advancing, with increasing clinical trials and novel applications emerging. However, the feasibility of DMT as an intervention for people living with functional neurological disorder (FND) has not been explored to date. This research aims to bridge the gap between current FND physiotherapy treatment options and the need for a holistic, integrative therapeutic model by 1) evaluating physiotherapist and lived experience perspectives of DMT and 2) co-designing a DMT intervention for people living with FND. Community and clinician perspectives will be captured via semi structured interviews conducted in both online and in-person formats. The co-design workshops will involve people living with early-stage FND, experiencing motor manifestations such as limb weakness, gait disturbances and impaired balance, together with dance therapists and allied health clinicians, and will be undertaken according to the UK Design Council's four stage, Double Diamond model. Workshops will *discover* the needs of this population and lay foundation for the *design, development* and refinement of a tailored DMT program. The outcomes of this research are expected to provide groundwork for the *delivery* of a feasibility trial aimed at evaluating a co-designed DMT intervention for the FND community within the next 18 months.

## Characterisation of inner ear organoids derived from human induced pluripotent stem cells

**Derek S. Delaney[1,2], Joey Lye[1,3], Fiona K. Leith[1,3], Sharon L. Redmond[1,3], Elaine Y.M. Wong[1,3,4]**
[1]Ear Science Institute Australia | *Nedlands, WA 6009, Australia*
[2]Curtin Medical Research Institute, Curtin University | *Bentley, WA 6102, Australia*
[3]Ear Sciences Centre, The University of Western Australia | *Nedlands, WA 6009, Australia*
[4]Curtin Medical School, Faculty of Health Sciences, Curtin University | *Bentley, WA 6102, Australia*

Sensorineural hearing loss is the leading cause of permanent deafness worldwide and is a highly debilitating disorder. It arises from the loss of inner ear hair cells and neurons which are responsible for the transduction of sound vibrations from the middle ear to signals transmitted to the brain. Despite recent innovations in hearing therapeutics, there are a lack of humanised *in vitro* models of the inner ear. To create a preclinically relevant model of the human inner ear, we have devised a method for creating inner ear organoids from human induced pluripotent stem cells (hiPSCs). We induce the differentiation of hiPSCs into inner ear organoids through the precise temporal manipulation of signalling pathways with drugs and small molecules that mimic the developmental timeline of the inner ear *in vitro*. To validate the derivation of hair cells and neurons, we performed immunohistochemistry and confocal imaging using markers specific to each cell type. Functional assessment of the inner ear organoids is demonstrated by FM1-43 accumulation, a dye that labels cells that actively release neurotransmitter. In conclusion, we demonstrate the differentiation of inner ear hair cells and neurons in inner ear organoids derived from hiPSC. Our organoid platform holds promise for the modelling of diseases, personalised medicine and high throughput screening of novel drug candidates against sensorineural hearing loss.

## Correlative analysis of metallomic gene expression and metal ion content within the mouse hippocampus

**Somayra S A Mamsa[1,2], Gaewyn Ellison[1,3], Julia Koehn[1], Keea Inder-Smith[1,4], Ross M Graham[1,4], Daryl L Howard[5], Mark J Hackett[1,3]**
[1]Curtin Medical Research Institute, Curtin University | *Bentley, WA 6102, Australia*
[2]School of Molecular Sciences, The University of Western Australia | *Crawley, WA 6009, Australia*
[3]School of Molecular and Life Sciences, Faculty of Science and Engineering, Curtin University | *Bentley, WA 6102, Australia*
[4]Curtin Medical School, Curtin University | *Perth, WA 6102, Australia*
[5]Australian Synchrotron, ANSTO | *Clayton, VIC 3168, Australia*

Brain metal homeostasis is essential for healthy neurological function, and aberrant brain metal homeostasis is a deleterious feature of several neurodegenerative diseases, such as Alzheimer's disease. Specific regions of the brain, such as the hippocampus and its subregions, are known to be enriched with transition metals including iron and zinc. However, neither the physiological need for localized enrichment, nor the mechanisms driving this enrichment, are well understood. In this study, we applied a multimodal template, incorporating elemental mapping using X-ray fluorescence microscopy with spatial transcriptomics, to reveal a molecular basis for metallomic heterogeneity across key subregions of the hippocampus. Our results demonstrate significant differences in iron and zinc content across hippocampal subregions, concurrent with regional enrichment of specific transcripts related to iron and zinc transport, storage, and regulatory proteins. In addition to providing novel biological insight, this study also provides an important template for integrating chemical and molecular analyses when studying the neurometallome.

## "How Did You Do It?": Ten Years of Partnership in Remote Neurological Care

**Melanie Clark[1,2,3], Brian Long[1], Lenni Duffield[4], Shenane Hogg[5], Christopher Kueh[6], Gareth Baynam[7,8], and Travis Cruickshank[3,9]**

[1]Neurosciences Unit, North Metropolitan Health Service Mental Health, Graylands Hospital | *Mount Claremont, WA 6009, Australia*
[2]School of Medical & Health Sciences, Edith Cowan University | *Joondalup, WA 6027, Australia*
[3]Perron Institute for Neurological & Translational Research | *Nedlands, WA 6009, Australia*
[4]Huntington's Australia | *Perth, WA 6009, Australia*
[5]Connectivity Traumatic Brain Injury Australia | *Nedlands, WA 6009, Australia*
[6]School of Arts and Humanities, Edith Cowan University | *Joondalup, WA 6027, Australia*
[7]Rare Care Centre, Child and Adolescent Health Service, Perth Children's Hospital | *Crawley, WA 6009, Australia*
[8]Lyfe Languages | *Perth, WA 6000, Australia*
[9]Centre for Precision Health, Edith Cowan University | *Joondalup, WA 6027, Australia*

A core tenant of public health is to provide equitable access to health care. Currently, a large Aboriginal kinship in far north Western Australia is affected by Huntington's disease. Huntington's disease is a rare, fatal, inherited neurological disorder. Due to the ongoing impacts of colonisation and living remotely, the affected kinship is largely unsupported and have not received adequate, culturally, and linguistically appropriate health care. The Neurosciences Unit, in collaboration with Huntington's Australia and Connectivity, have conducted remote mobile multidisciplinary Huntington's clinics in the East Kimberley. The clinics have been successful and are expanding beyond Huntington's to include education and assessment of other neurological conditions.

The Far North Mobile Neurological Clinic:

- Offers specialist neurology, psychiatry, social work, and speech pathology assessment and support to improve the capacity of those affected by Huntington's,
- Identifies at-risk individuals,
- Increases health literacy and access to treatment and prevention services,
- Upskills local medical, allied health, and support work staff,
- Improves medical and social outcomes,
- Identifies and refers individuals living with neurological conditions other than Huntington's disease,
- Provides education on Traumatic Brain Injury recognition and prevention, and
- Reduces social isolation and increases wellbeing and social connection for those with neurological disorders.

The Far North Mobile Neurological Clinic is the only mobile neurological care clinic in Australia. Initiation of clinics on Country required a collaborative effort across government and non-government services with kinship representatives for over a decade. The process, barriers, and facilitators impacting the development and delivery of the mobile clinics are discussed.

## AUS-mTBI: Leveraging digital technology to predict outcomes after mild traumatic brain injury

**Jemma Keeves[1,2,3], Sarah Hellewell[1,2], Deval Mehta[4], Xin Zhang[4], Zongyuan Ge[4], Roley Myers[1,2], Jacinta Thorne[1,2], Rachel Singer[1,2], Jade Guarnera[5], Katherine Kenyon[5], Kylie Rixon[6], Rachel Cavanagh[7], Rebecca Richardson[7,8], Darcy Moore[7], AUS-mTBI Investigators, Nick Rushworth[9], Jesse Young[10,11,12,13], Michael Makdissi[14,15,16], Tamara Ownsworth[6,17], Karen Barlow[18,19], Kate Curtis[7,20], Elizabeth Kendall[6], Trish Ratajczak[21], Gary Mitchell[22,23,24,25], George Charalambous[26], Natasha Lannin[27,28], Karen Caeyenberghs[5], Beth Armstrong[29], Jennie Ponsford[30,31], Patrick Kwan[3,27,28], Kirsten Vallmuur[24,32], Vicki Anderson[33,34], Belinda Gabbe[3], Melinda Fitzgerald[1,2,35]**

[1]Curtin Medical Research Institute, Faculty of Health Sciences, Curtin University | *Bentley, WA 6102, Australia*
[2]Perron Institute for Neurological & Translational Science | *Nedlands, WA 6009, Australia*
[3]School of Public Health & Preventive Medicine, Monash University| *Melbourne, VIC 3004, Australia*
[4]AIM for Health Lab, Faculty of IT, Monash University | *Melbourne, VIC 3008, Australia*
[5]Cognitive Neuroscience Unit, School of Psychology, Deakin University | *Burwood, VIC 3125, Australia*
[6]School of Applied Psychology, Griffith University | *Southport, QLD 4222, Australia*
[7]Faculty of Medicine & Health, The University of Sydney, Susan Wakil School of Nursing & Midwifery | *Camperdown, NWS 2050, Australia*
[8]RPA Green Light Institute, Sydney Local Health District | *Camperdown, NWS 2050, Australia*
[9]Brain Injury Australia | *Sydney, NSW 2112, Australia*
[10]Centre for Health Equity, Melbourne School of Population & Global Health, The University of Melbourne | *Parkville, VIC 3052, Australia*
[12]Centre for Adolescent Health, Murdoch Children's Research Institute | *Parkville, VIC 3052, Australia*
[12]School of Population & Global Health, The University of Western Australia | *Crawley, WA 6009, Australia*
[13]National Drug Research Institute, Curtin University | *Bentley, WA 6102, Australia*
[14]La Trobe Sport & Exercise Medicine Research Centre, La Trobe University | *Bundoora, VIC 3086, Australia*
[15]Olympic Park Sports Medicine Centre | *Melbourne, VIC 3000, Australia*
[16]Australian Football League | *Docklands, VIC 3008, Australia*
[17]Hopkins Centre, Inclusive Futures, Griffith University | *Nathan, QLD 4111, Australia*
[18]Acquired Brain Injury in Children Research Program, Queensland Children's Hospital | *Brisbane, QLD 4101, Australia*
[19]Centre for Children's Health Research, University of Queensland, | *Brisbane, QLD 4101, Australia*
[20]Emergency Services, Illawarra Shoalhaven Local Health District, Wollongong Hospital | *Wollongong, NSW 2500, Australia*
[21]Murdoch University | *Murdoch, WA 6150, Australia*
[22]Emergency & Trauma Unit, Royal Brisbane & Women's Hospital | *Brisbane, QLD 4029, Australia*
[23]Royal Brisbane Clinical Unit, University of Queensland | *Brisbane, QLD 4029, Australia*
[24]Jamieson Trauma Institute| *Brisbane, QLD 4029, Australia*
[25]Queensland Rugby Union | *Newmarket, QLD 4051, Australia*
[26]Curve Tomorrow | *Melbourne, VIC 3000, Australia*
[27]Department of Neurosciences, School of Translational Medicine, Monash University | *Melbourne, VIC 3004, Australia*
[28]Alfred Health | *Melbourne, VIC 3000, Australia*
[29]School of Medical & Health Sciences, Edith Cowan University | *Joondalup, WA 6027, Australia*
[30]Turner Institute for Brain & Mental Health, School of Psychological Sciences, Monash University | *Melbourne, VIC 3800, Australia*
[31]Monash Epworth Rehabilitation Research Centre, Epworth Healthcare | *Melbourne, VIC 3002, Australia*
[32]Centre for Healthcare Transformation, Australian Centre for Health Services Innovation | *Brisbane, QLD 4006, Australia*
[33]Psychology Service, The Royal Children's Hospital | *Melbourne, VIC 3052, Australia*
[34]Clinical Sciences Research, Murdoch Children's Research Institute | *Melbourne, VIC 3052, Australia*
[35]Connectivity Traumatic Brain Injury Australia | *Nedlands, WA 6009, Australia*

In Australia, 180,000 mild traumatic brain injuries (mTBI) occur annually. ~20-50% of people experience symptoms that persist for months-to-years after injury. mTBI management is variable, with limited capacity to predict delayed recovery. AUS-mTBI is using app-based technology to identify key predictors of mTBI recovery in the Australian population with the objective of delivering improved care advice.

AUS-mTBI participants aged five and over who sustained mTBI in the previous 14 days, self- or proxy-report demographic, injury, health status, symptom burden, and care management data through the HeadCheck app. Post-concussion symptoms and recovery are assessed using the Rivermead Post-Concussion Questionnaire (adults) and Post-Concussion Symptom Inventory (5–18y), administered at day 1,3,5,7,14,30 and then fortnightly for three months post-injury and monthly thereafter until symptom resolution. Data analysis uses machine learning, including Random Survival Forest models for adults and children to identify recovery predictors.

HeadCheck(v3.0.3) has recruited 524 participants to-date (55.4% children, 44.6% adults). 51.2% identify as male, 52.0% sustained mTBI from non-sporting mechanisms, most commonly falls and 60.3% attended hospital post-mTBI. Preliminary models suggest that the strongest predictors of recovery in adults are injury mechanism, age, history of previous mTBI and healthcare interactions (e.g. hospital care, follow up treatment)(C-index 0.57±0.09). For children, the strongest predictors of recovery are age, socioeconomic status, peri-injury neck pain, resilience and injury mechanism (C-index 0.48±0.05).

Predicting delayed recovery after mTBI is challenging. Using machine learning to identify modifiable factors, AUS-mTBI will help shape future directions of HeadCheck and inform improved data-driven care pathways.

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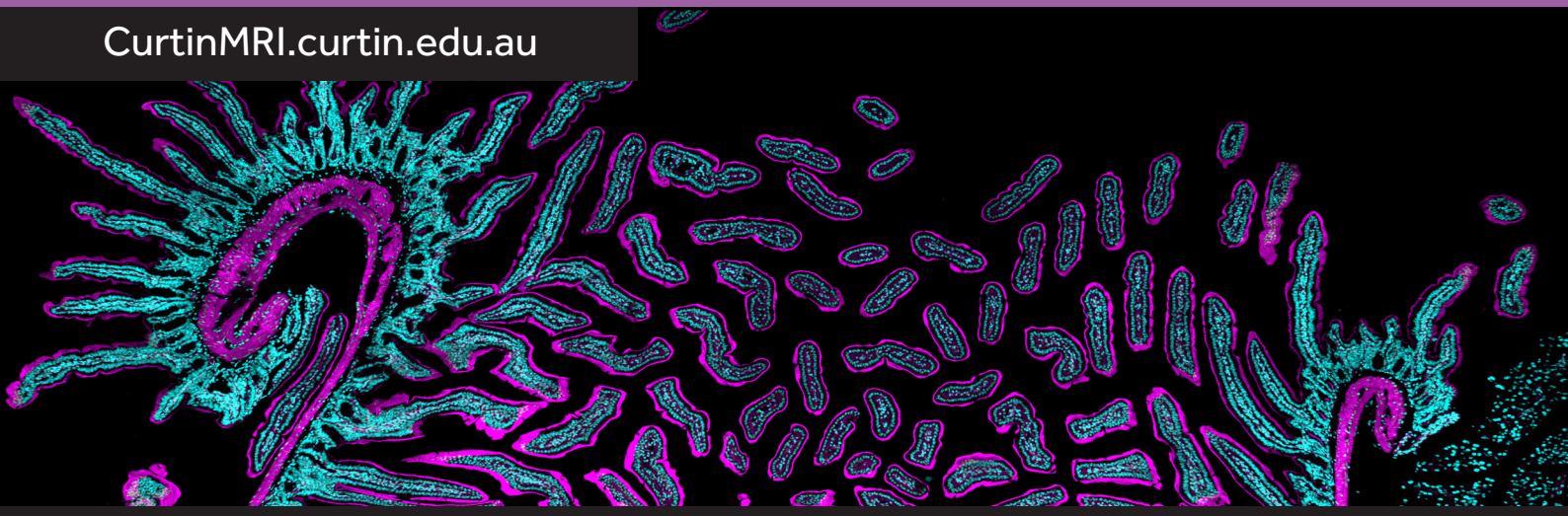


## From discovery to clinical impact.

The Curtin Medical Research Institute (Curtin MRI) stands at the forefront of discovery, turning scientific insight into real-world health solutions. From discovery to clinical impact, it brings together brilliant minds dedicated to transforming lives through innovation, collaboration, and a relentless pursuit of a healthier future for all.

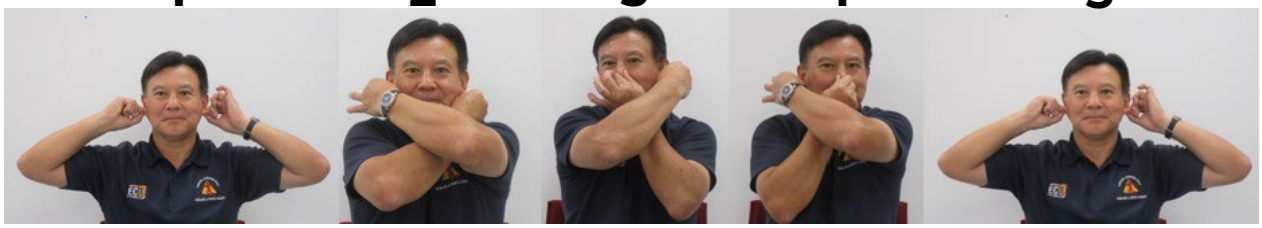
***Make tomorrow better.***

# BRAIN EXERCISES

If you wish to complete the brain exercises demonstrated by Professor Ken Kosaka, we encourage you to incorporate them into your daily routine. These coordinated movement tasks are designed to stimulate attention, memory, and cognitive flexibility through simple, practical activities that can be performed in any setting.

## Exercise One

1 2 3 4 5



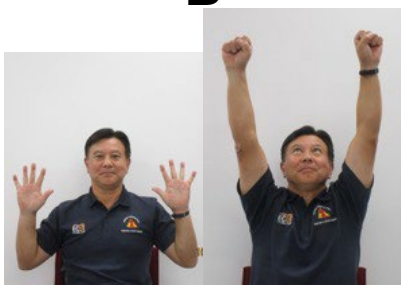
**Count: Ichi, Ni, San, Shi, Go**

## Exercise Two

A

Close › Open

B



Open › Close

C

Right: Close › Open
Left: Open › Close

**Count: Ichi, Ni, San, Shi, Go, Roku**

## Exercise Three

A

Close › Open

B

Open › Close

C

Right: Close › Open
Left: Open › Close

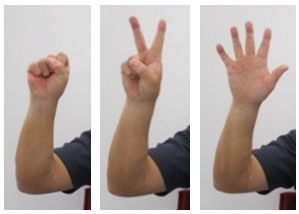
**Count: Ichi, Ni, San, Shi, Go, Roku**

## Exercise Four

1 2 3 4

**Count: 100/99, ...90 / 100, 97, ...73**

## Exercise Five



Rock, Scissors, Paper

Paper, Rock, Scissors

1

2

3

## Exercise Six

1 2

Arms: Open Legs: Open

Arms: Close Legs: Close

1 2

Arms: Open Legs: Close

Arms: Close Legs: Open

## Exercise Seven

1 2 3 4 5 6

Arms: Open, Close, Open, Close, Open, Close

Legs: Open, Close, Close, Open, Close, Close

## Exercise Eight & More

- Throw a ”ball” with one hand, Catch it with two hands
- Throw and catch a “ball”, while counting from 100, 97, 94, 91, …. or 100, 93, 86, 79, ….
- Throw a “ball” with one hand, Clap once, and Catch it
- Throw a “ball” with one hand, Clap twice (three, four, five times), and Catch it
- Throw a “ball”, Clap once (twice), and Catch it, while saying names of countries (animals, fruits, …, …)
- Dribble a “ball” with right and left hand alternatively, while saying names of countries (animals, fruits, …, …)