Brain Wiring Disorders
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Our Future on the Neuro-Frontier
International Brain Initiative
Australian Brain Alliance
How is the brain formed and wired to function?
The corpus callosum connects the two brain hemispheres.
How do human brain wiring disorders occur and how do they affect brain function?

Humans ↔ Animals
Macroscale ↔ Microscale

MRI Brain Imaging (Humans and Animal Models)
Cognitive neuropsychological testing and animal behaviour
Genetics and gene function at a cellular, molecular, developmental level
Corpus callosum malformations

- Occurs in 1:3000 births
- Associated with around 300 different congenital syndromes
- Some individuals have a corpus callosum malformation in isolation

Can cause deficits in:
- Sensory and motor function
- Language development
- Social interaction
**International Research Consortium for the Corpus Callosum and Cerebral Connectivity**

IRC5 Working Groups:
- Research Imaging
- Clinical imaging and brain dysmorphology
- Neuropsychology and Psychiatry
- Genetics
- Fetal and perinatal diagnosis

Paediatric neurologists/geneticists/clinical psychologists/neuroradiologists

Rick Leventer & Paul Lockhart, Melbourne
Lynn Paul, Caltech, Pasadena
Tania Attie-Bitach, Paris
George McGillivray & Simone Mandelstam, Melbourne
Elliott Sherr, San Francisco
Christel Depienne, Strasbourg
Fernanda Tovar-Moll, Rio de Janeiro
Warren Brown, Los Angeles
Linda Richards, Brisbane

*Discovering the causes, improving diagnosis, treating the individual and supporting families.*
DCC mutations in ACC and congenital mirror movement disorder

Marsh et al., 2017, *Nature Genetics*
People with complete agenesis of the corpus callosum display an unfused septum.
Common developmental mechanisms in corpus callosum formation, ventricular size, megalencephaly and brain cancer

Nuclear Factor One (Nfi) genes

- Transcription factors
- 5’-TTGGCNNNNNGCCAA-3’
- *Nfia*, *Nfib*, *Nfic* and *Nfix*

DNA binding and dimerisation

transactivation and repression

Highly conserved

member specific

Nfi research team

K-S Chen  Jonathan Lim
Dr Jens Bunt  Caity Bridges  Yunan Yi

Queensland Brain Institute
NFI’s regulate proliferation and differentiation by binding directly to DNA.
NFI in human developmental disorders

• Overlapping brain phenotype:
  – Dysgenesis of the corpus callosum
  – Ventriculomegaly
  – Megalencephaly
  – Developmental delay / intellectual disability

• *NFIA*: 1p32-p31 deletion syndrome

• *NFIX*: Malan syndrome & Marshall-Smith syndrome
Nuclear Factor One (NFI) genes regulate corpus callosum formation

Normal (green)
Agenesis of the CC (*)
Dysgenesis of the CC (red)

Developmental Genome Anatomy Project Harvard Medical School
NFI regulates interhemispheric fissure remodelling.
Fgf8-NFI mediated interhemispheric remodelling

Gobius et al., 2016, *Cell Reports*
NFI in human developmental brain disorders

- NFIA point mutation
  - Negishi et al., 2015

- NFIA deletion
  - Koehler et al., 2007

- NFIA translocation

- NFIA deletion

- Control

- NFIB deficiency
  - Sajan et al., 2013; Schanze, Bunt et al. AJHG in press

Lu et al., 2007
NFI genes in childhood and adult brain cancer

Image courtesy of Dr Lindy Jeffree Radiopaedia.org

Kok-Siong Chen

Dr Jens Bunt

Queensland Brain Institute
Implication of NFI in tumours

- **ETMR** (Spence 2014, Lambo 2016)
- **Medulloblastoma** (Genovesi 2013, Lastowska 2013 Wu 2012)
  - *Nfi’s are* common targets in insertional mutagenesis SHH mouse model
  - *Nfia* loss associated with more aggressive tumours
  - NFIA expression correlates with lower grade/better outcome
  - NFIA expression associated with a transition from oligodendroglioma to astrocytoma morphology
  - *Nfi’s are* common targets in insertional mutagenesis glioma mouse models

- Adenoid cystic carcinoma
- ER-negative breast carcinoma
- Lymphoma/leukemia
- Melanoma
- Non-small cell lung carcinoma
- Osteosarcoma
Current Lab Members:
Jens Bunt
Rodrigo Suárez
Ilan Gobius
Peter Kozulin
Timothy Edwards
Caitlyn Bridges
Ryan Dean
Jonathan Lim
Laura Fenlon
Kok-Siong Chen
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Annalisa Paolino
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Yunan Ye
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Cancer Project Collaborators:
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Dietmar Hutmcher & Phong Tan, QUT
Marcel Kool & Sander Lambo, DKFZ, German Cancer Research Centre
Hani Ariffin, Malaya Cancer Research Institute
*Wesley Medical Research, Queensland Brain Tumour Bank.
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Brain Injured Children Aftercare Recovery Endeavours
Promoting Australia’s current and future neuroscience research capabilities that are driving engagement in the global effort to understand the brain and to treat neurological diseases and mental illnesses.
• Founded in February 2016 by the Australian Academy of Science Brain and Mind Committee to transform the brain research sector in Australia.

• The Alliance aims to secure a commitment to an Australian Brain Initiative.

• Supported by major scientific societies, brain research institutes and neurotechnology companies.
Australian Brain Initiative
Cracking the brain’s code.

A proposal for an Australian Brain Initiative (ABI) is under development by members of the Australian Brain Alliance. Here we discuss the goals of the ABI, its areas of research focus, its context in the Australian research setting, and its necessity for ensuring continued success for Australian brain research.
Australian Brain Initiative

Cracking the brain’s code. Neuroengineering Australia’s Future

- Develop advances in the understanding of brain function
- Create advanced industries, develop and capitalize on new technologies.
- Identify causes, and develop treatments for, debilitating brain disorders.
- Produce high-impact transdisciplinary collaborations that will increase our understanding of the brain to produce social, health and economic outcomes for all Australians.
- Develop discoveries in a responsible manner with ethical oversight and public engagement.
National network established November 2017 with support from the Theo Murphy Initiative
Australian Brain Alliance
Brains at the Dome 2017
A workshop on international brain initiatives.
International Brain Initiative

- Formalised in the ‘Canberra Declaration’
- Signed by 10 country brain projects and international brain organisations on 7 December, 2017
• Public and Parliamentary Friends of Science panel discussions on Brain Science and Technology
• 2-day neurotechnology showcase in the Mural Hall at Parliament House
• Book launch by Professor George Paxinos FAA
• Promotional and information materials distributed to parliamentarians
• One-on-one meetings with MPs and Senators, Ministers and Shadows
The Australian Brain Alliance has now met with more than 75 politicians at #BrainsOnTheHill.
#crackthebrainscode  #auspol
Become a Brain Champion

Sign up at
www.brainalliance.org.au
Emergence of global brain projects

Coordination needed to maximize impact and efficiency, reduce potential redundancy across global brain projects
Catalyzing and advancing ethical neuroscience research through international collaboration and knowledge sharing, by uniting diverse ambitions to expand scientific possibility, and disseminating discoveries for the benefit of humanity.
INTERNATIONAL BRAIN INITIATIVE

International Brain Bash

MARRIOT MARQUIS BALLROOM F

NOV 03 6:30p UNTIL 9:00p

#BrainBashSfN

DRINKS & LIGHT HORS D'OEUVRES WILL BE SERVED

LAUNCH PARTY for the IBI website & CELEBRATION of this global collaboration