

Brain Wiring Disorders

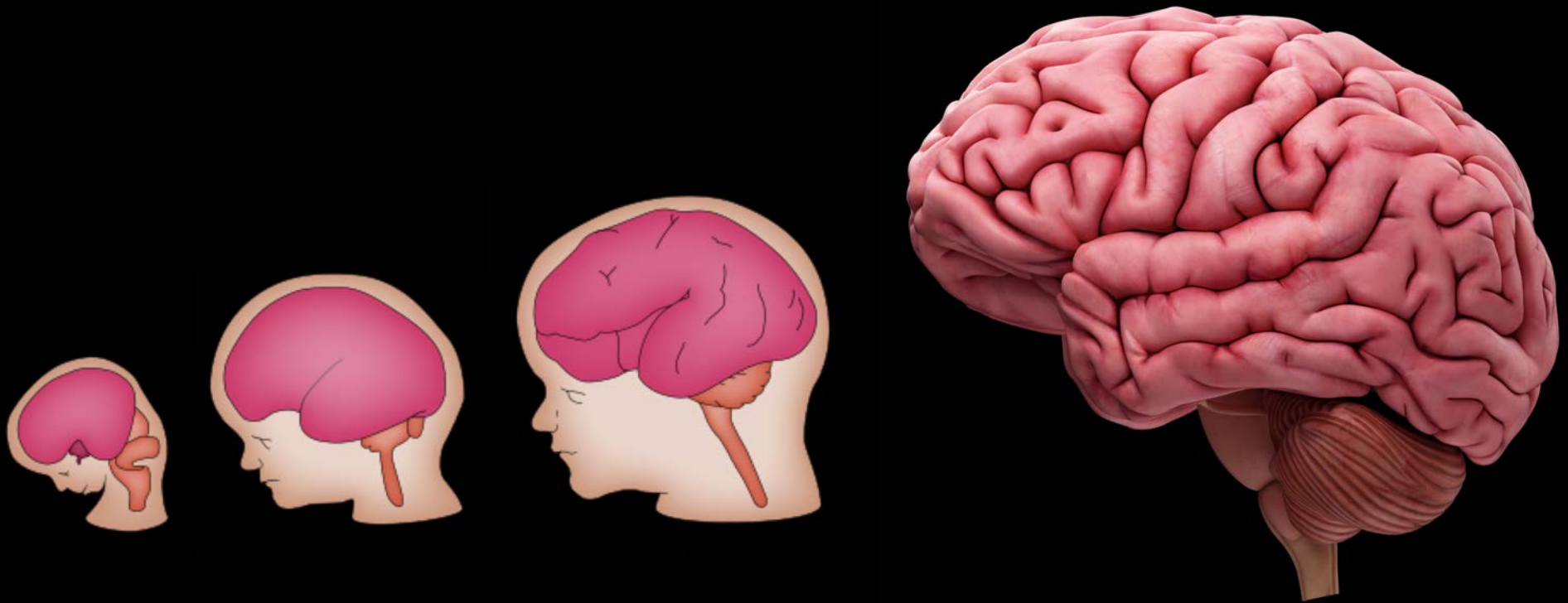
Linda J. Richards, PhD, FAA, FAHMS

Queensland Brain Institute,
University of Queensland,
Brisbane, Australia

Our Future on the Neuro-Frontier



How is the brain formed and wired to function?



Brain Development

Birth

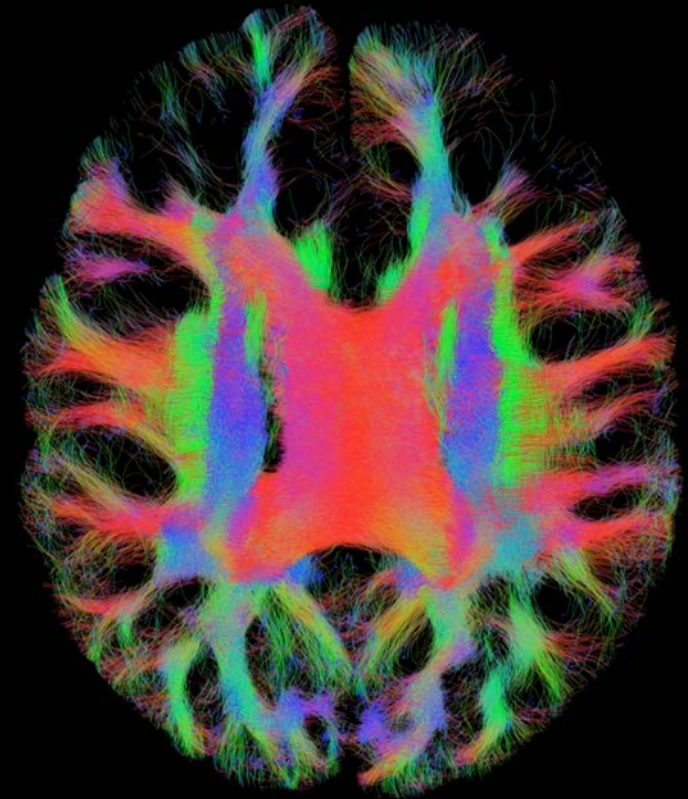
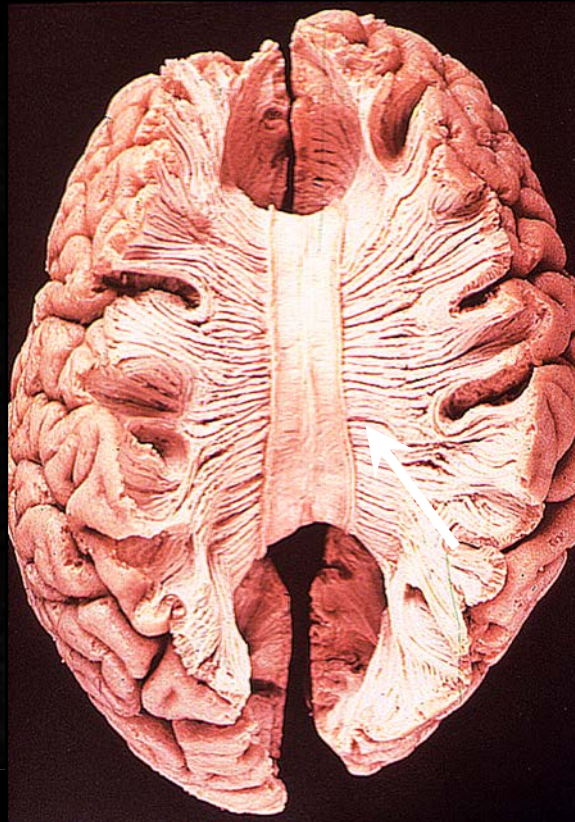
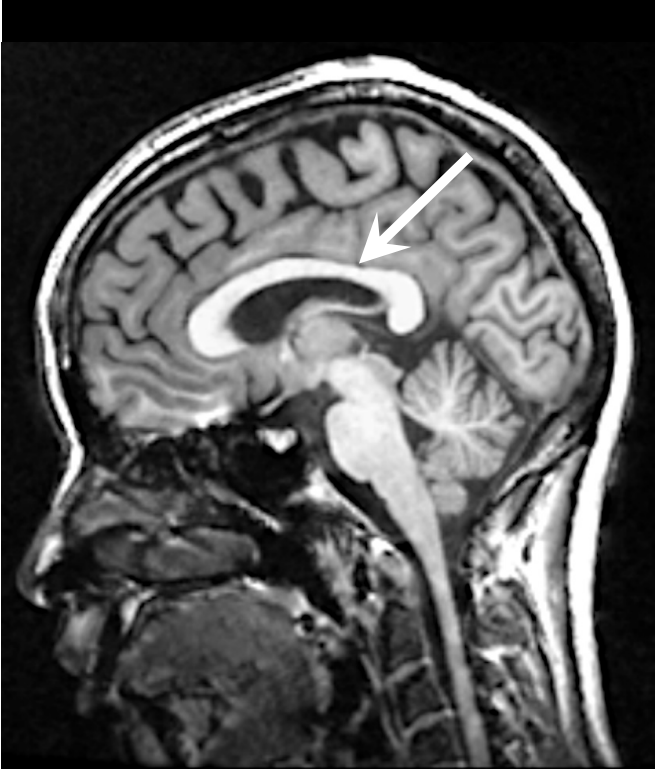


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The corpus callosum connects the two brain hemispheres



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How do human brain wiring disorders occur and how do they affect brain function?



advocating | uniting | supporting



Humans ↔ Animals

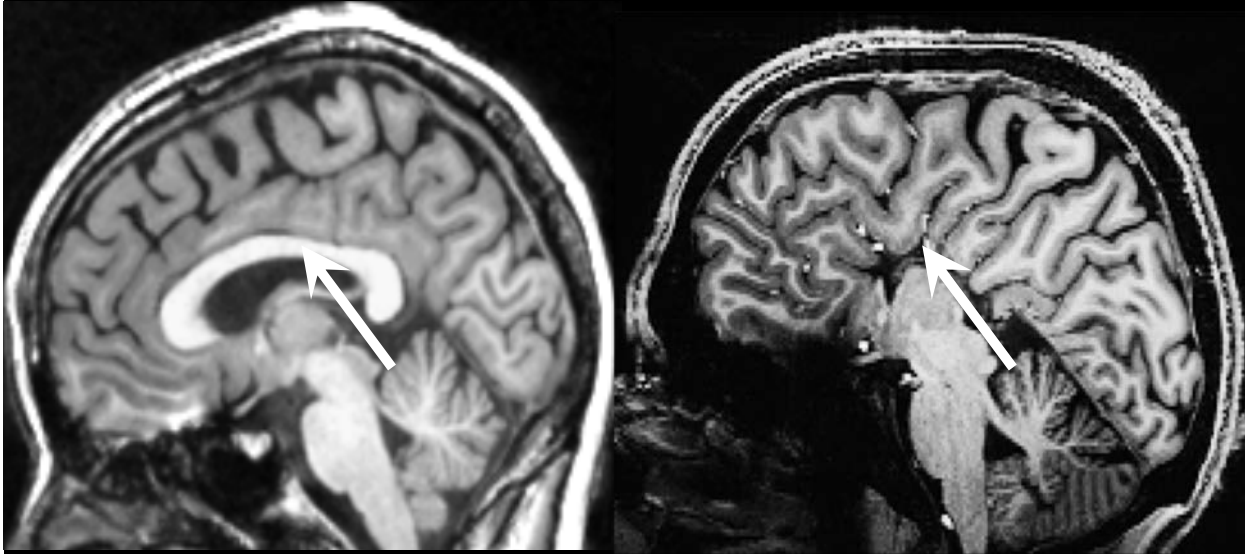
Macroscale ↔ Microscale

MRI Brain Imaging (Humans and Animal Models)

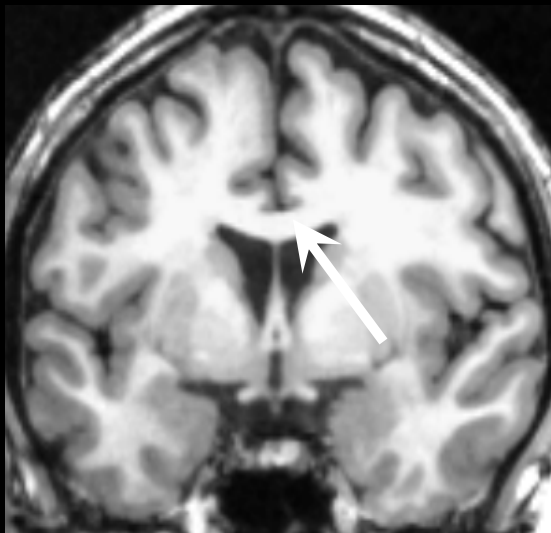
Cognitive neuropsychological testing and animal behaviour

Genetics and gene function at a cellular, molecular, developmental level

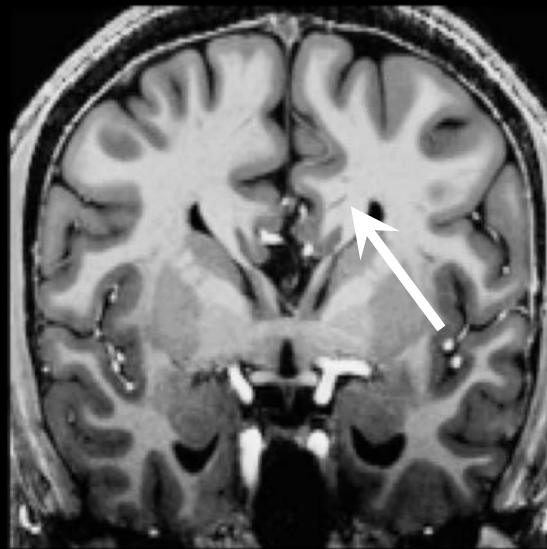
Corpus callosum malformations



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



Control



Agenesis of the corpus callosum

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



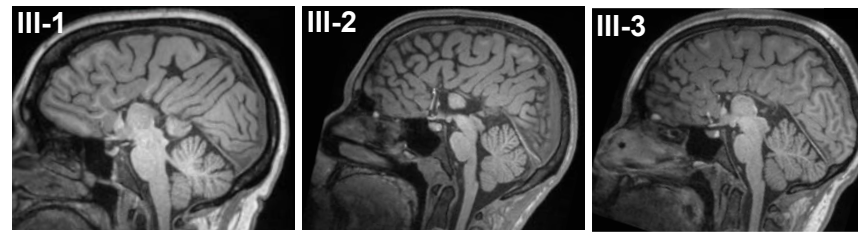
Rick Leventer & Paul Lockhart, Melbourne
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Christel Depienne, Strasbourg
Fernanda Tovar-Moll, Rio de Janeiro
Warren Brown, Los Angeles
Linda Richards, Brisbane



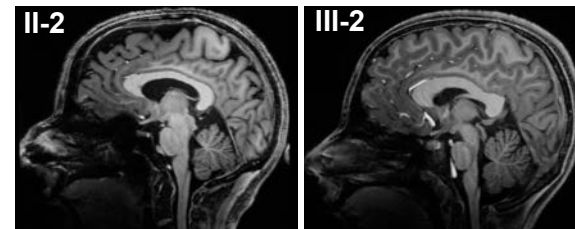
*Discovering the causes, improving diagnosis,
treating the individual and supporting families.*

DCC mutations in ACC and congenital mirror movement disorder

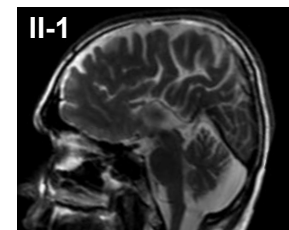
CMM Family 2



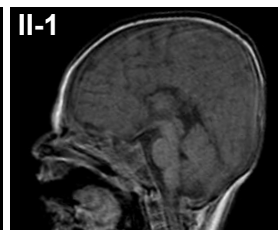
CMM Family 4



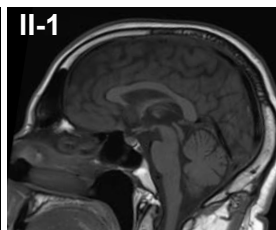
CMM Family 6



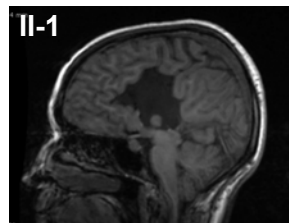
CMM Family 8



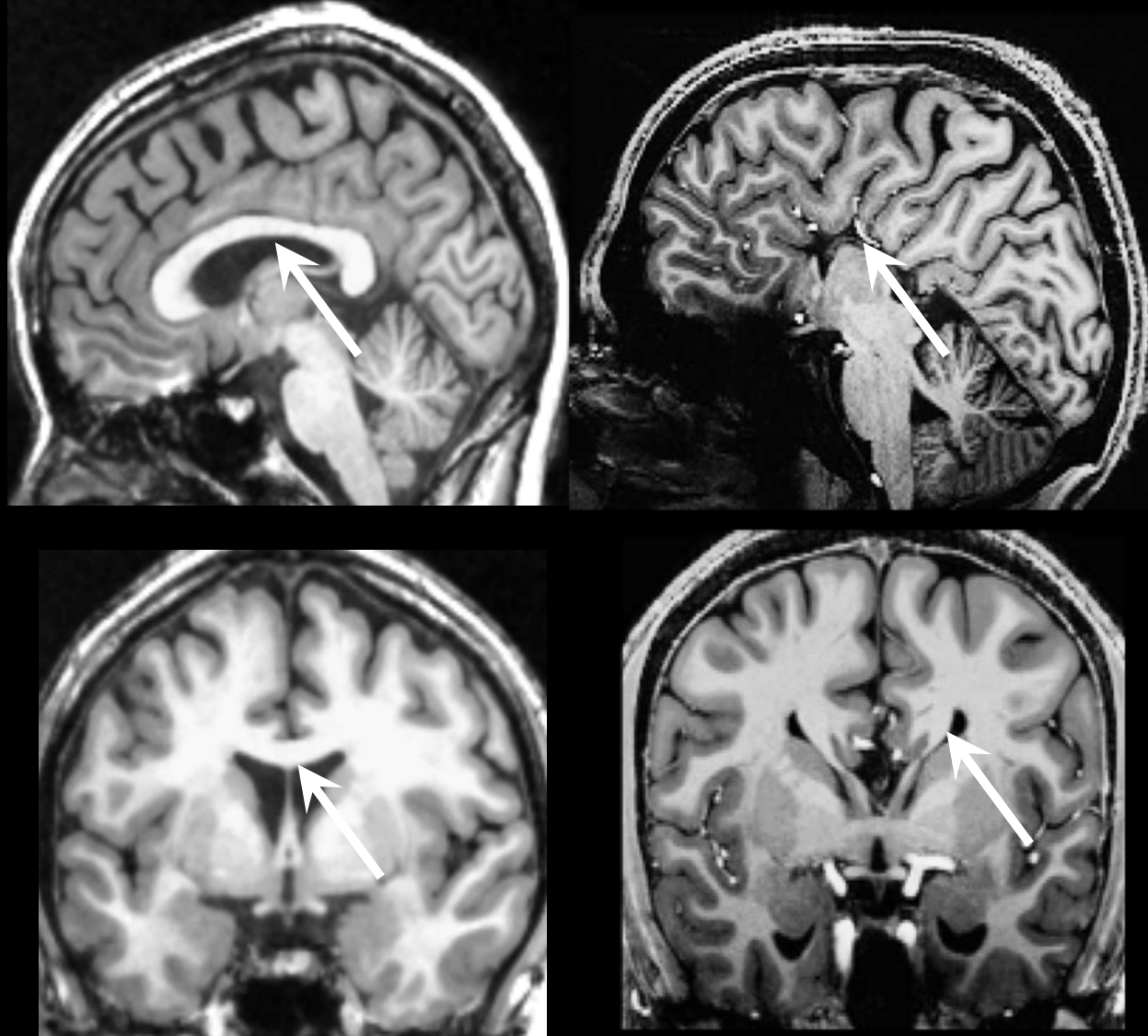
CMM Family 5



CMM Family 9



People with complete agenesis of the corpus callosum display an unfused septum



Control

Agenesis of the corpus callosum

Gobius et al., 2016, *Cell Reports*

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*

Nfi research team



Dr Jens Bunt



K-S Chen



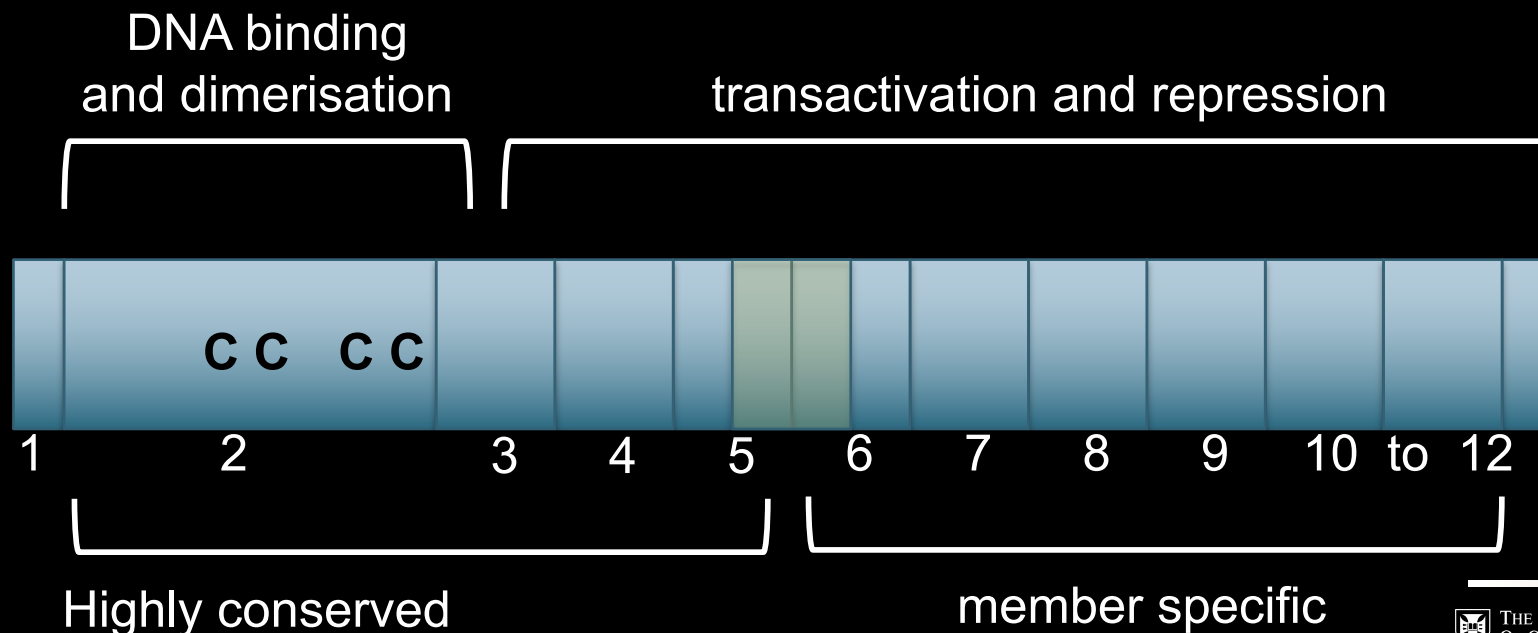
Jonathan Lim



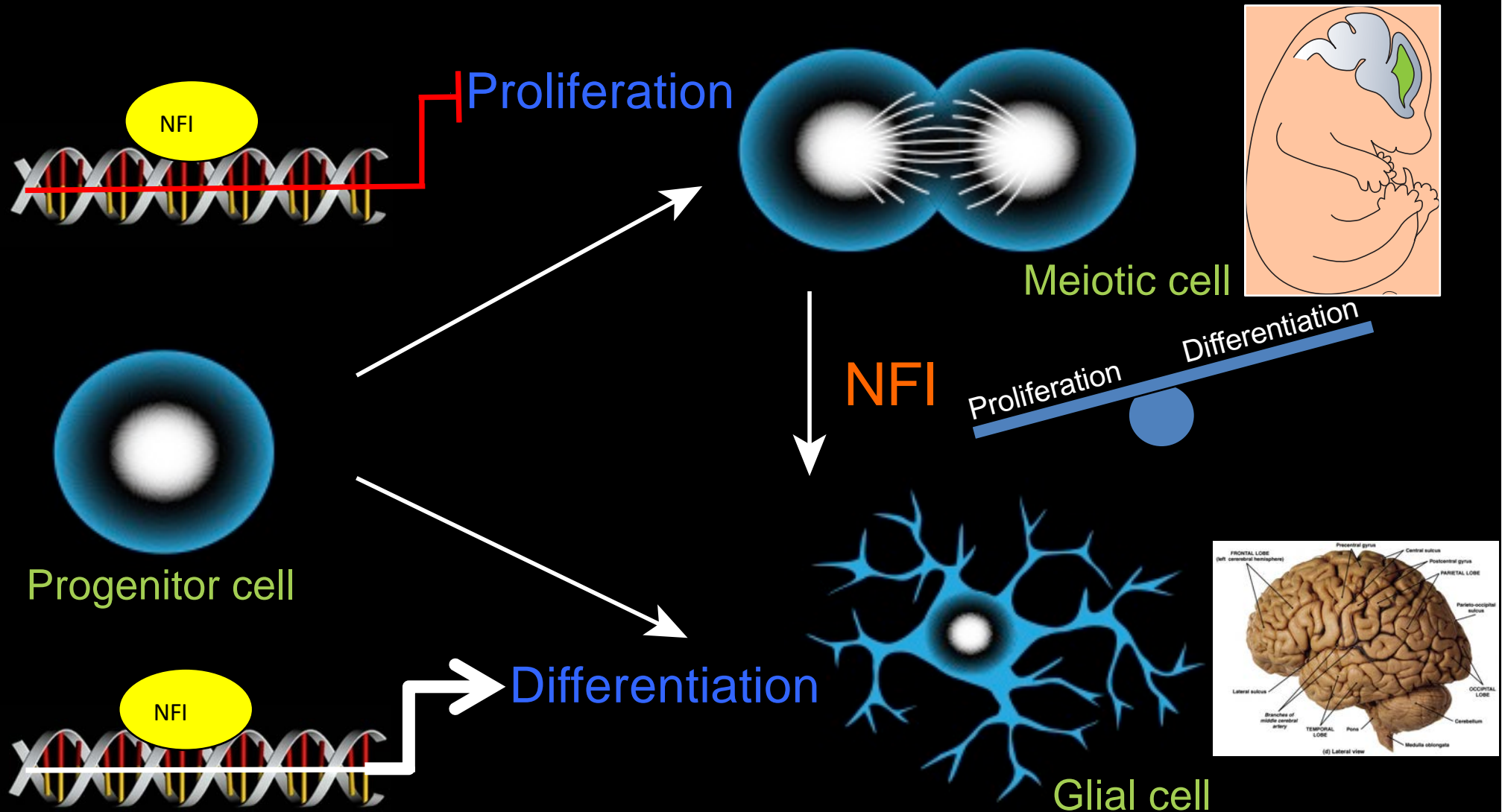
Caity Bridges



Yunan Yi



NFI's regulate proliferation and differentiation by binding directly to DNA

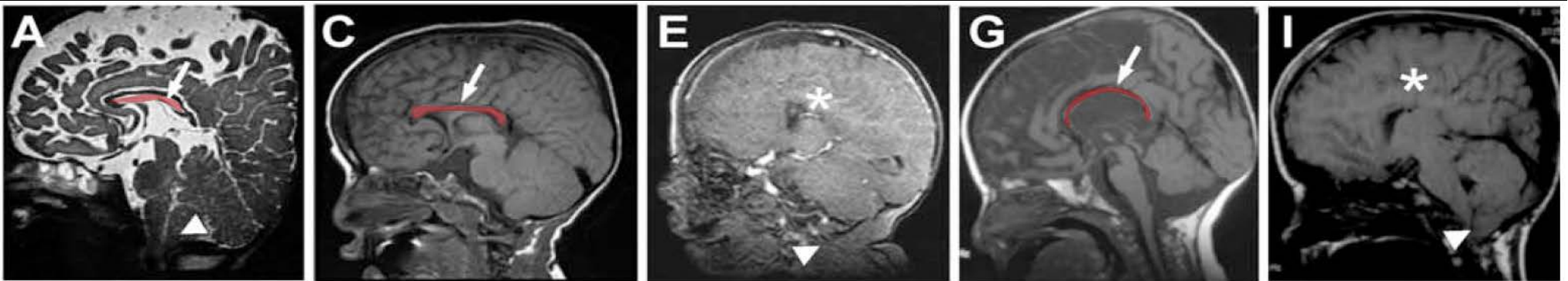
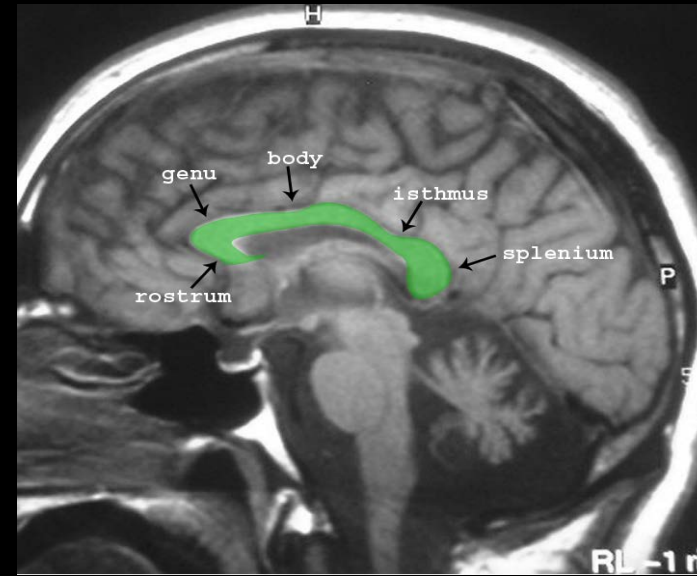


NFI in human developmental disorders

- 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

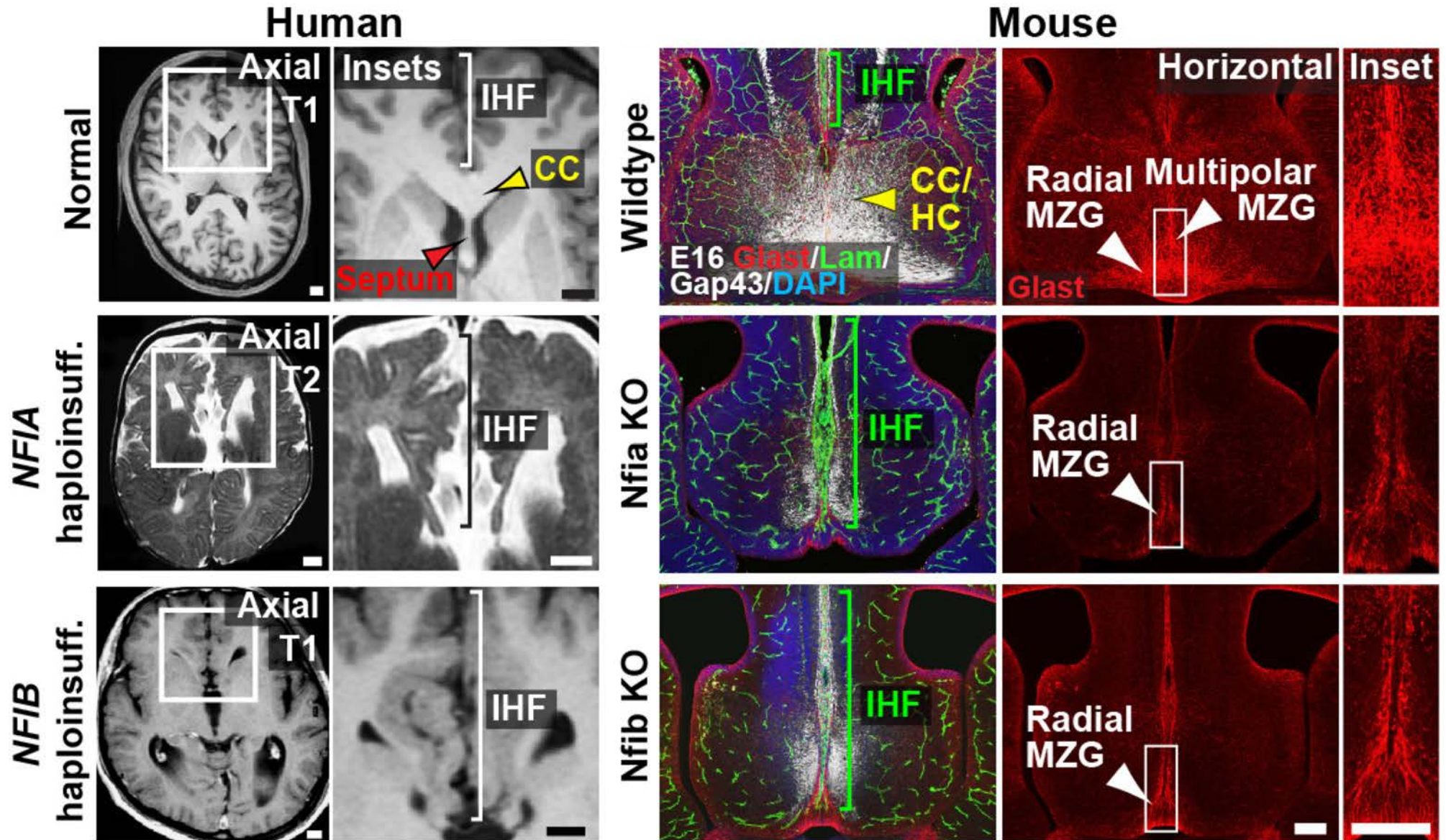
Nuclear Factor One (NFI) genes regulate corpus callosum formation

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

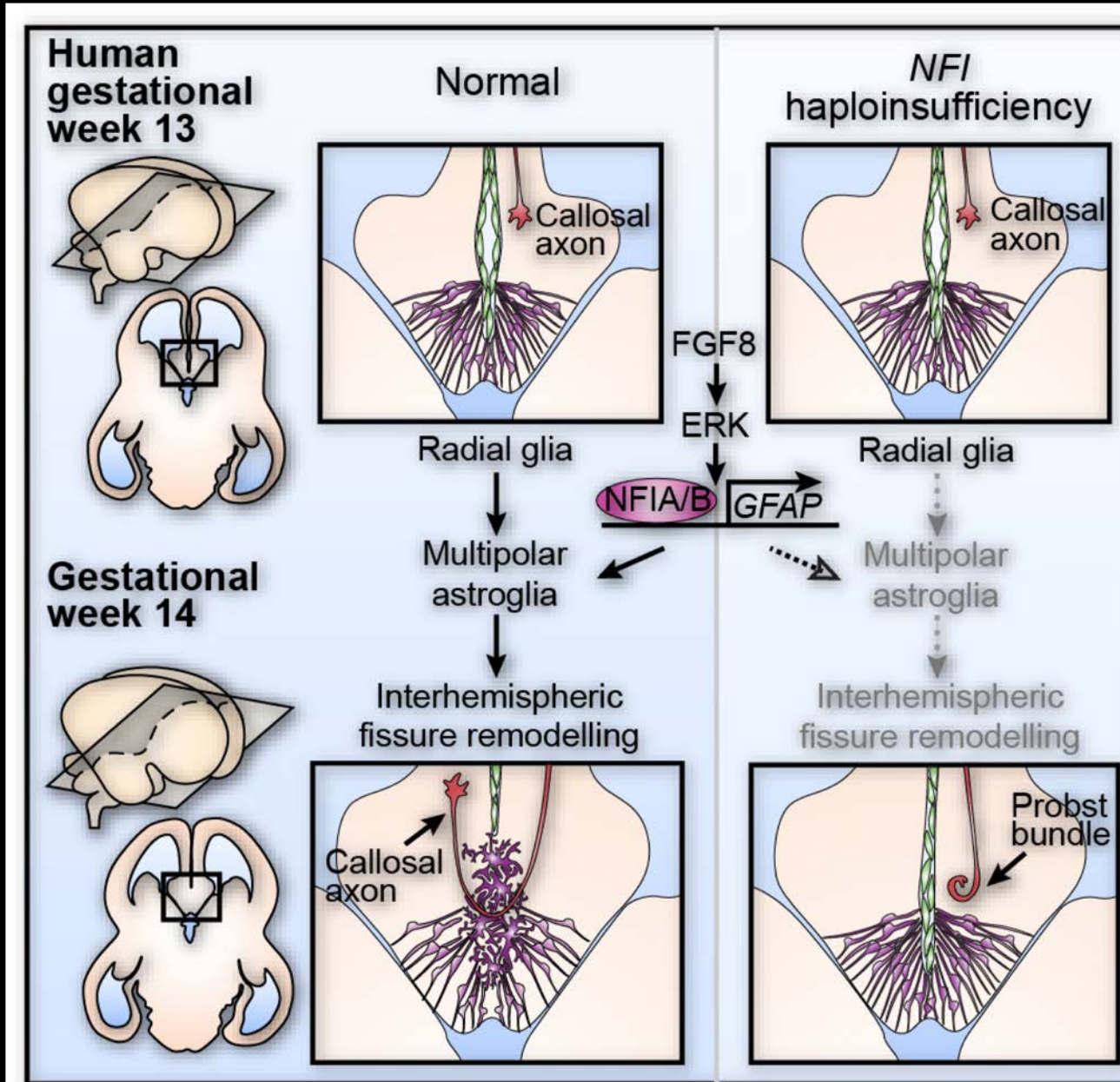


Lu et al., PLoS Genet. 2007 May 25;3(5):e80.
Developmental Genome Anatomy Project Harvard Medical School

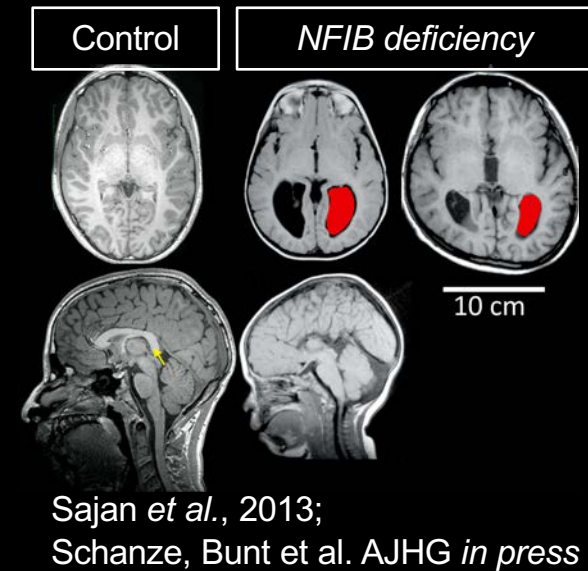
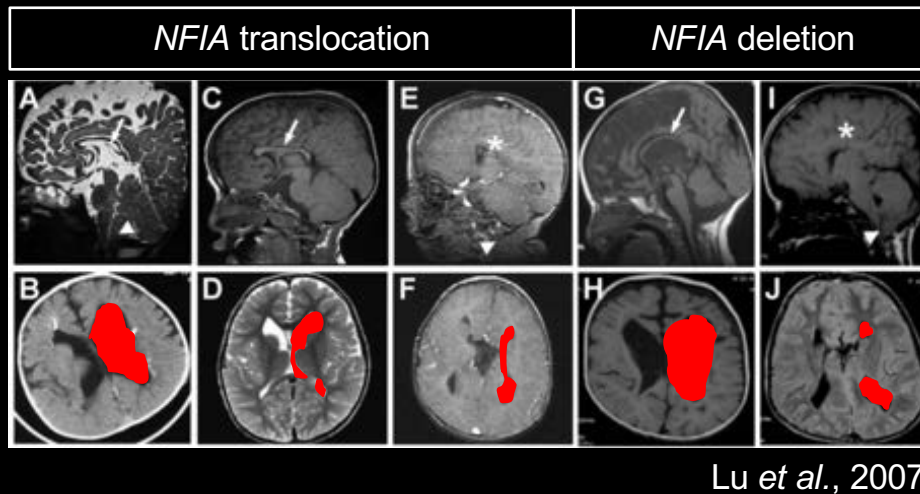
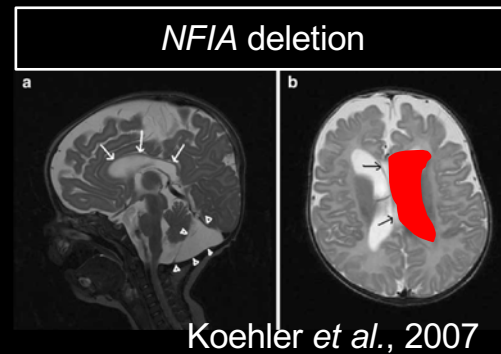
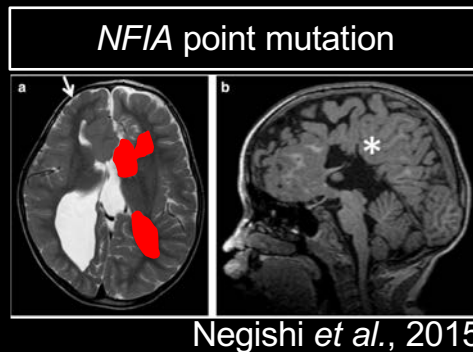
NFI regulates interhemispheric fissure remodelling



Fgf8-NFI mediated interhemispheric remodelling



NFI in human developmental brain disorders



NFI genes in childhood and adult brain cancer

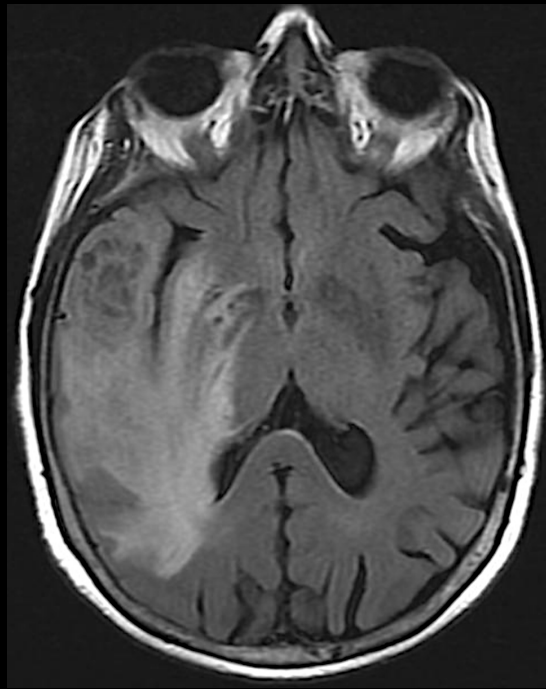
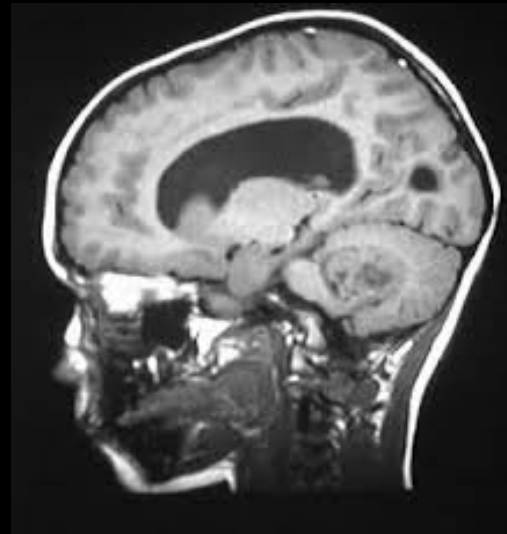
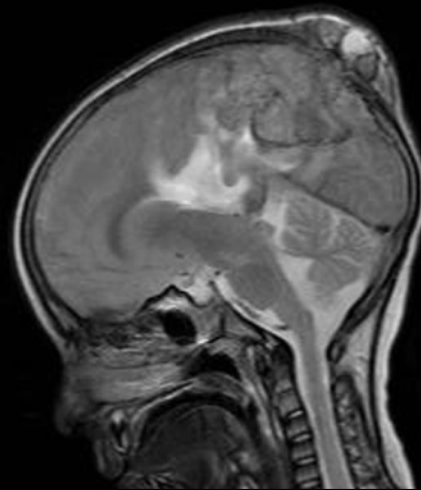


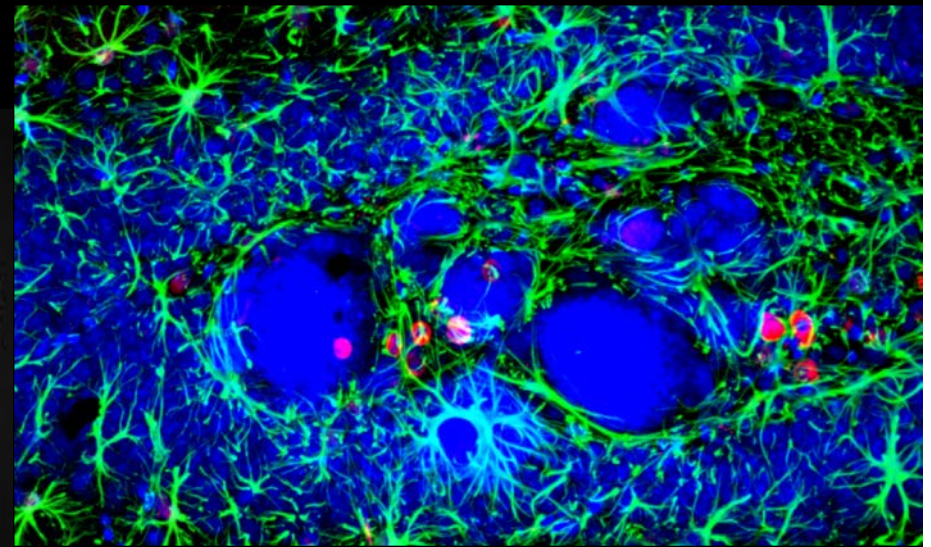
Image courtesy of Dr Lindy Jeffree
Radiopaedia.org



Kok-Siong
Chen

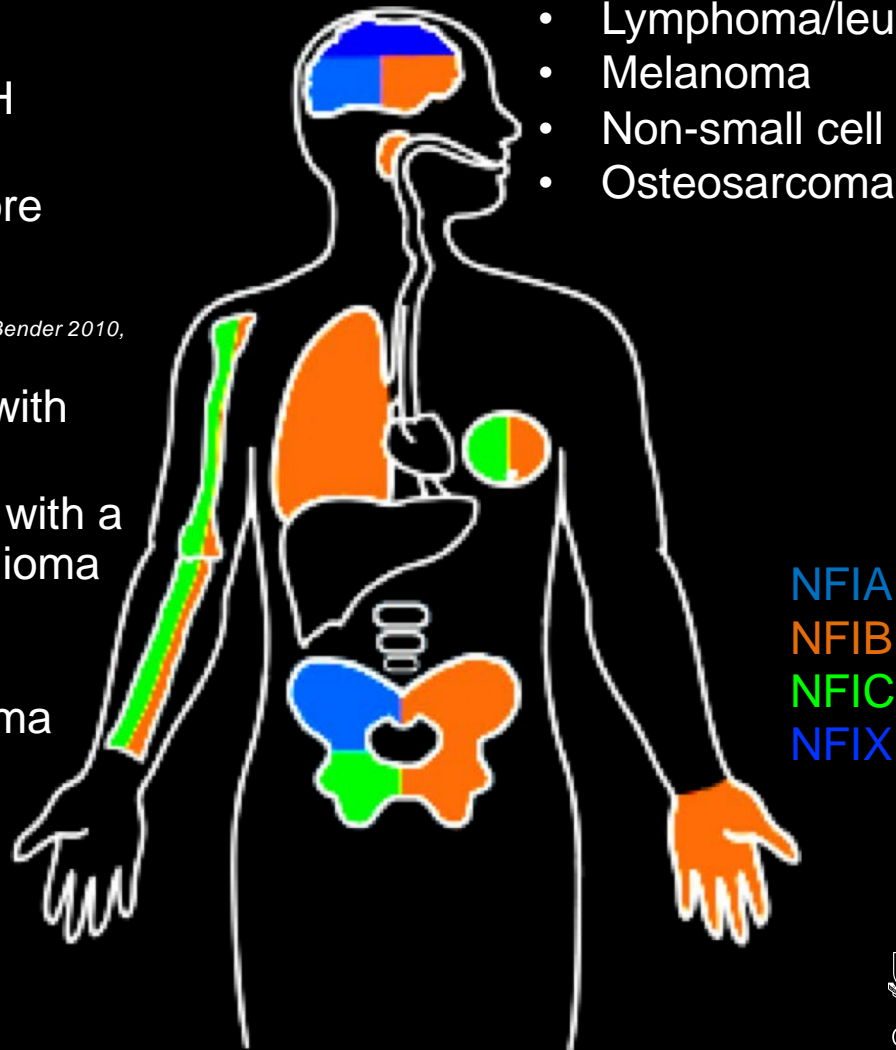


Dr Jens Bunt



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
- Glioma (*Song 2010, Glasgow 2014, Johansson 2006, Bender 2010, Vyazunova 2014, Cancer 2016*)
 - 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



Acknowledgements

The University of Queensland, Queensland Brain Institute

Current Lab Members:

Jens Bunt
Rodrigo Suárez
Ilan Gobius
Peter Kozulin
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Queensland Brain Institute

Brain Injured Children Aftercare Recovery Endeavours

Our Future on the Neuro-Frontier



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.



Overview

- 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
Alliance

Neuron
NeuroView

Australian Brain Alliance

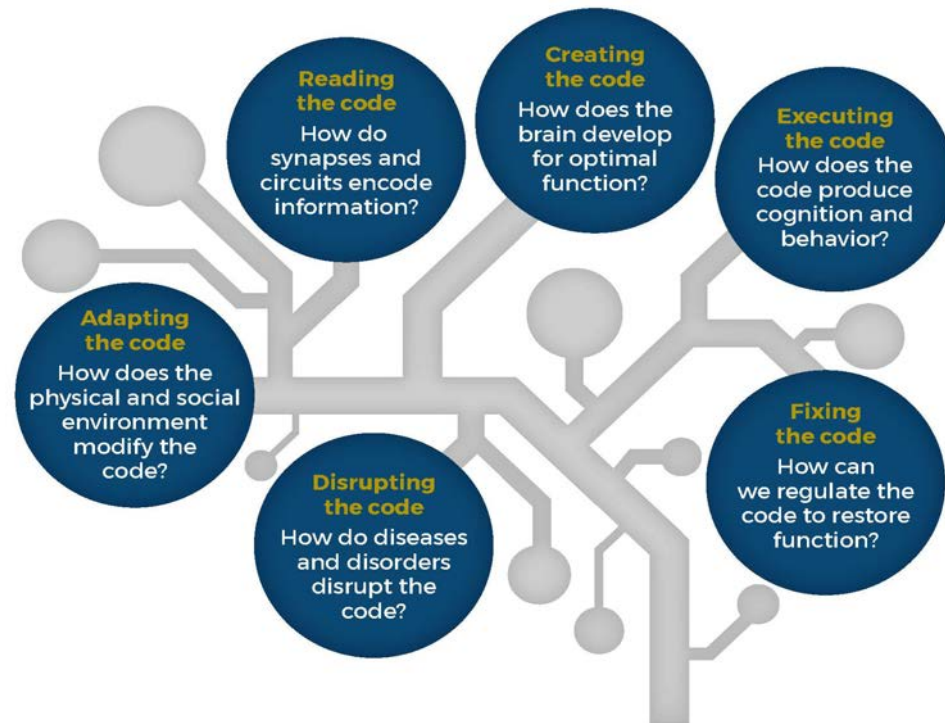
Australian Brain Alliance Steering Committee*

*Correspondence: richards@uq.edu.au

<http://dx.doi.org/10.1016/j.neuron.2016.10.038>

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. Neuron 92, November 2, 2016 © 2016



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.

Our sponsors





International Brain Initiative

- Formalised in the 'Canberra Declaration'
- Signed by 10 country brain projects and international brain organisations on 7 December, 2017

World's Brain Initiatives Move Forward Together

A meeting of representatives from some of the world's major brain research projects, hosted by the Australian Academy of Science in Canberra, has made a declaration to establish an International Brain Initiative.

The declaration, made by representatives from Japan, Korea, Europe, the United States of America and Australia, is designed to speed up progress on 'cracking the brain's code'.

'Researchers working on brain initiatives from around the world recognise that they are engaged in an effort so large and complex that even with the unprecedented efforts and resources from public and private enterprise, no single initiative will be able to tackle the challenge to better understand the brain,' according to the declaration.

President of the Australian Academy of Science, Professor Andrew Holmes, said the announcement of an International Brain Initiative was one of the most exciting days of his presidency to date.

CRACK
• THE
• BRAIN'S
• CODE



26-28
MARCH
2018

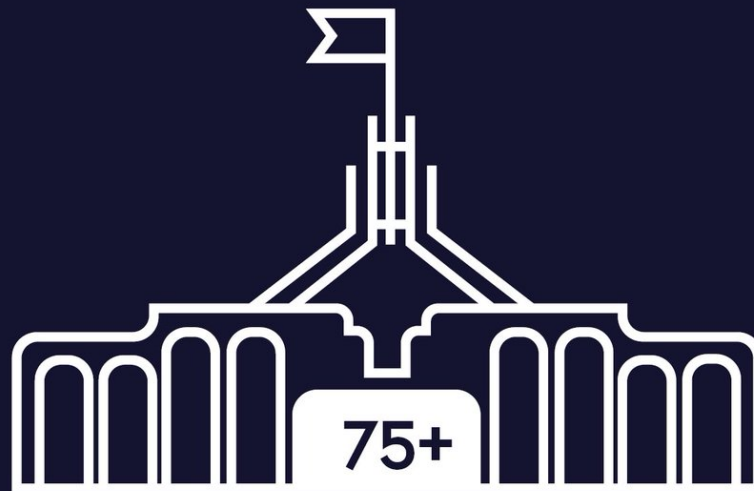


BRAINS ON THE HILL

- 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



CRACK.....
...THE.....
...BRAIN'S..
.....CODE

brainscode.org.au



Become a Brain Champion

Sign up at
www.brainalliance.org.au



Help Crack the Brain's Code

The human brain is staggeringly complex, and Australian neuroscientists and psychologists have a long and distinguished record of achievement in unravelling its mysteries and creating new applications and technologies.

Australia - we can Crack the Brain's Code and revolutionise our healthcare and education system, and create advanced neurotechnologies inspired by the brain.

We have the right people to crack the brain's code, but we need your support by becoming a Brain Champion.

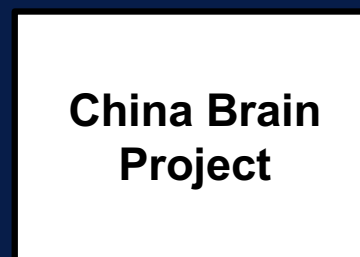
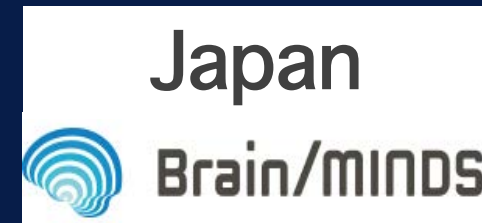
Sign me up



IBI INTERNATIONAL BRAIN INITIATIVE



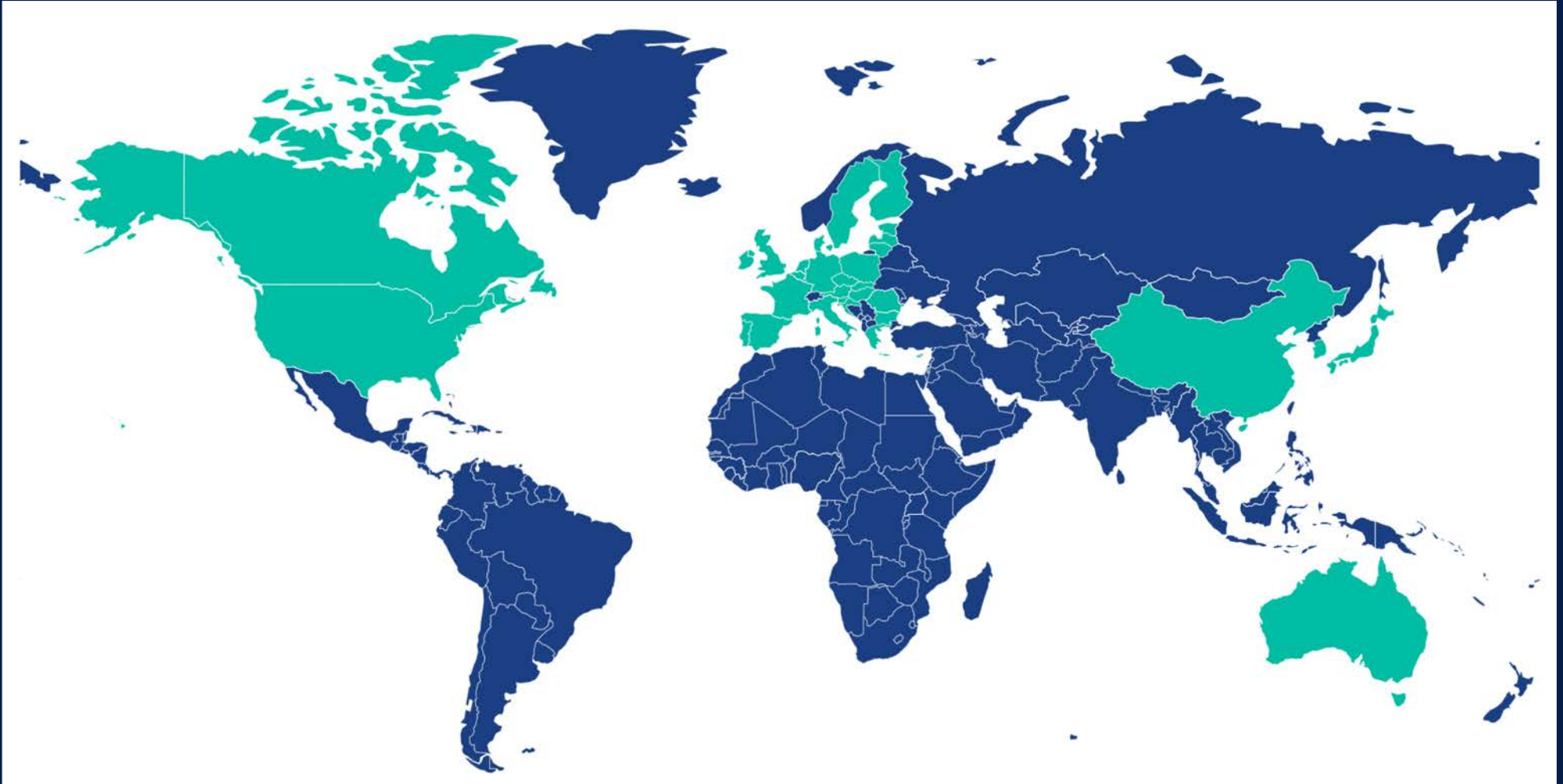
Emergence of global brain projects



**Coordination needed to maximize impact and efficiency,
reduce potential redundancy across global brain projects**



INTERNATIONAL BRAIN INITIATIVE



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.

IBI INTERNATIONAL
BRAIN
INITIATIVE

International Brain Bash

MARRIOT MARQUIS

NOV

6:30p UNTIL 9:00p

BALLROOM F

03

#BrainBashSfN

DRINKS & LIGHT
HORS D'OEUVRES
WILL BE SERVED

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