

WashU MEDICINE



# Land acknowledgement

We begin by acknowledging that we are on the traditional homelands of the Osage Nation, Missouriia, and Illini Confederacy, who were removed unjustly, and that we in this community are beneficiaries of that removal. We honor them as we live, work, and study here at Washington University.

Erlanger & Gasser Nobel



Invention of PET scanner



1970s: Development of criteria-based psychiatric diagnosis



1944

1950

1969

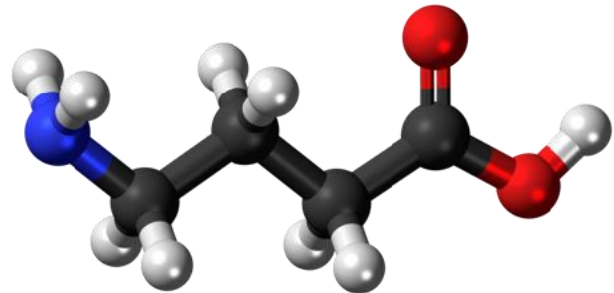
1975

1980

1982

1986

Discovery of GABA



Founding of McDonnell Centers for Systems Neuroscience and Cellular and Molecular Neurobiology

Launch of excitotoxicity field

Establishment of Clinical Dementia Rating Score

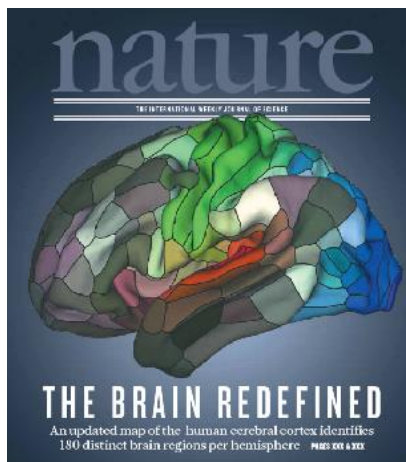
Levi-Montalcini & Cohen Nobel, discovery of nerve growth factor





Publication of Human  
Connectome Project

FDA approval of drug  
for SOD/ALS



Debut of laser  
therapy to open BBB

Development of focused  
ultrasound liquid biopsy  
for brain tumors

2001

2013

2017

2021

2023

2024

Identification  
of propofol target

FDA approval of  
Ipsihand, rehab tool  
for stroke recovery

Continuation of clinical trials  
to prevent Alzheimer's disease

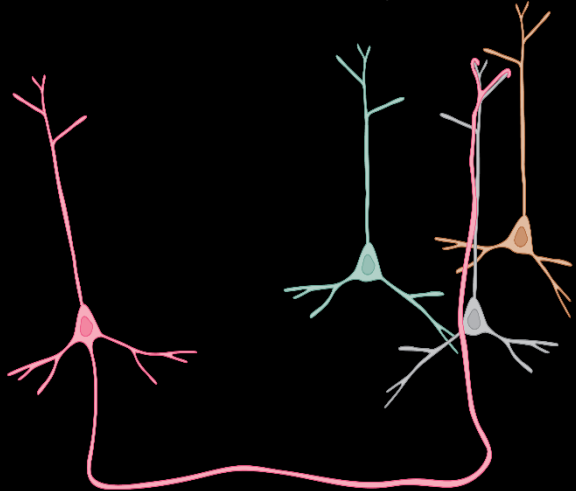
Description of  
brain networks  
(default mode network)

First report of  
blood test for AD



- Executive Function
- Social Cognition
- Complex attention and motivation
- Language, expression and creativity
- Emotions, Mood
- Self/Brain-Body experience

# Cognition, Behavior & Brain-Body Experience

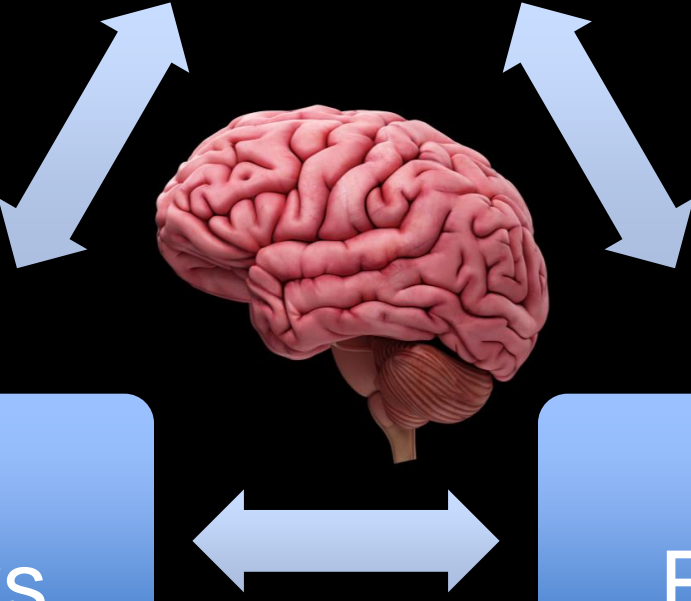


- Learning/information encoding
- Memory
- Sensory Perception, sensory integration
- Motor Function/Coordination
- Sleep
- Brain-Body signaling (sickness behavior, neuroimmune signaling, brain lymphatics, pain)



## Brain Networks

## Brain Function



Across micro-meso scales:  
local, long-range and brain-wide

- Anatomy, development and plasticity (across temporal scales)
- Circuit Modulation
- Communication between cells/ glial function

Neural systems & theory  
Psychiatric neuroscience & therapeutics  
Pain & peripheral nervous system  
Circuits, neuroplasticity & behavior  
Brain tumor biology  
Developmental disorders & neurogenomics  
Neurodegeneration & neuroimmunology



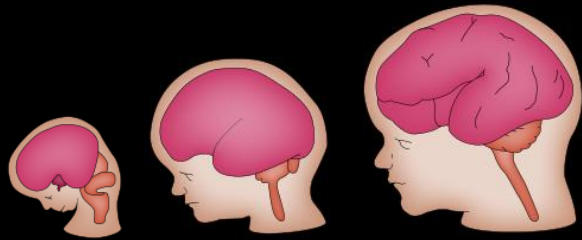


Developmental disorders & neurogenomics

Can we understand and treat childhood disorders such as:

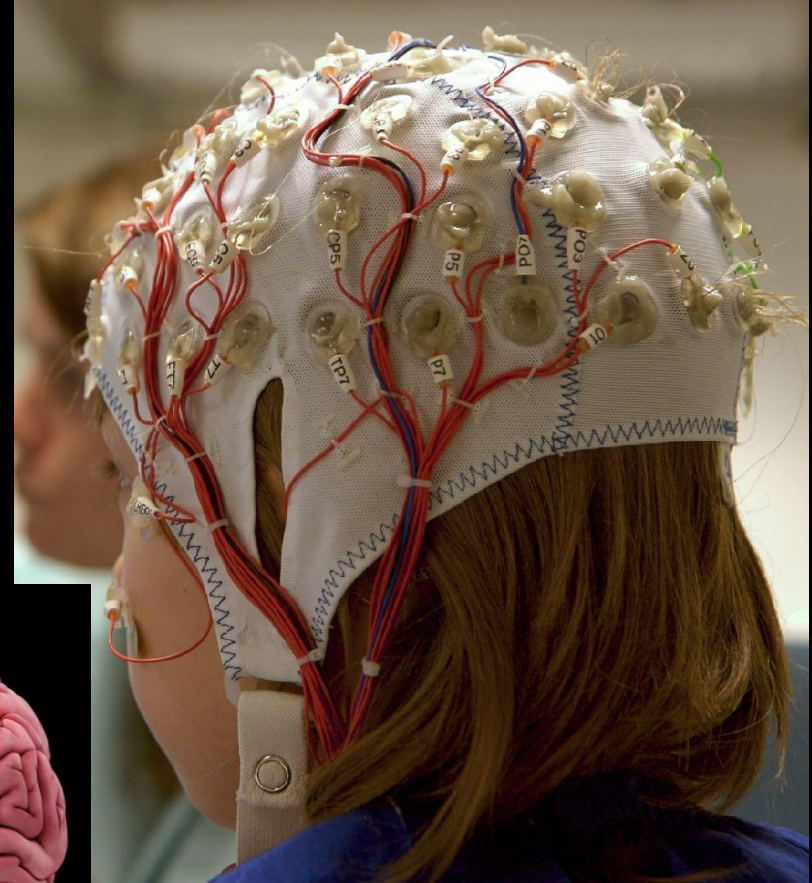
- Intellectual Disability
- Epilepsy
- Cerebral Palsy
- Autism
- Developmental delays in language & reading
- Sensory deficits in vision & hearing

LIFELONG DISABILITY



*Brain Development*

Birth







Hemispheric connections  
*Disorders of the corpus callosum*



Protein function in neurodevelopment  
*Angelman syndrome*



Epigenomics and gene regulation  
*Rett syndrome & overgrowth syndromes*

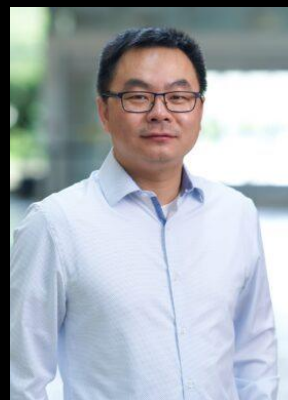
Auditory system  
*Deafness and communication disorders*



Neuroimmunology  
*Brain development*



Computational models of behavior  
*Autism spectrum disorder*



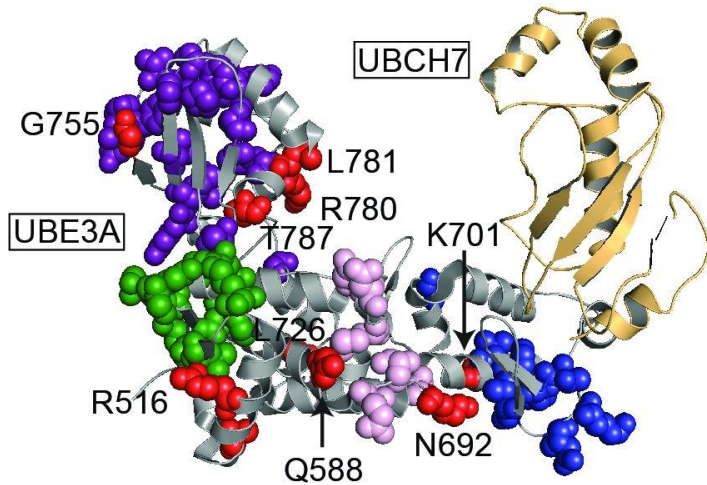
Somatosensory system  
*Fragile X syndrome*





# Yi Lab

*How do different disorders arise from variants in the same gene?*



*UBE3A (gray) and its partner enzyme (gold), with disease-related variants labeled*

Variants that **inhibit** UBE3A cause Angelman Syndrome

Variants that **boost** UBE3A cause autism spectrum disorder

**How do they each affect cellular function and brain development?**



## **Yi Lab Approach »**

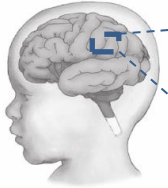
Methods to analyze protein function » Tools to assess developmental consequences » Interventions to correct dysfunction



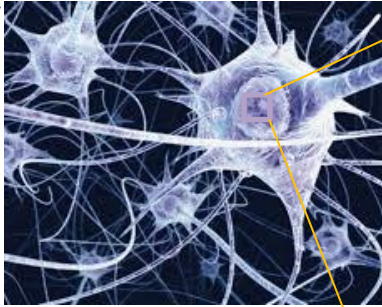
# Gabel Lab

*How do epigenetic mechanisms govern the development of the brain?*

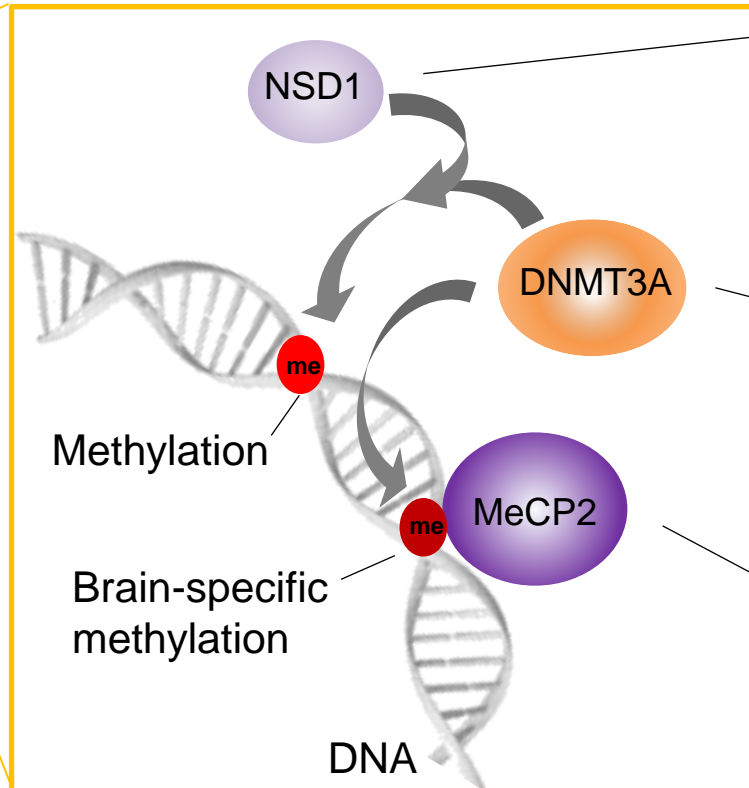
Developing brain



Billions of brain cells



Nucleus of a developing brain cell



NSD1 disrupted in  
**Sotos Syndrome**



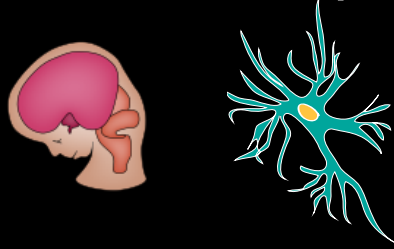
DNMT3A disrupted  
**Tatton Brown  
Rahman Syndrome**



MeCP2 disrupted  
**Rett Syndrome**



Early brain development



Brain Wiring



How is the brain wired for function  
and how plastic are these networks?

Cognitive Function



# Early brain development



Human



Brain Wiring



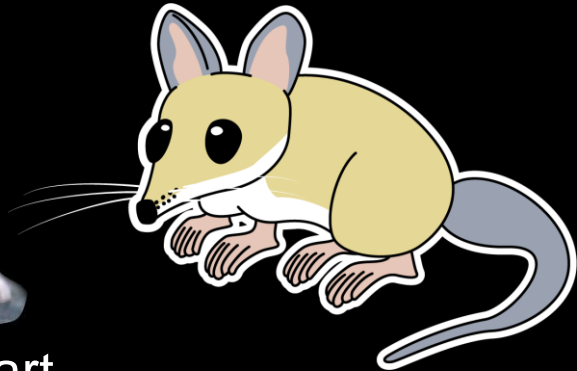
Cognitive Function



Mouse

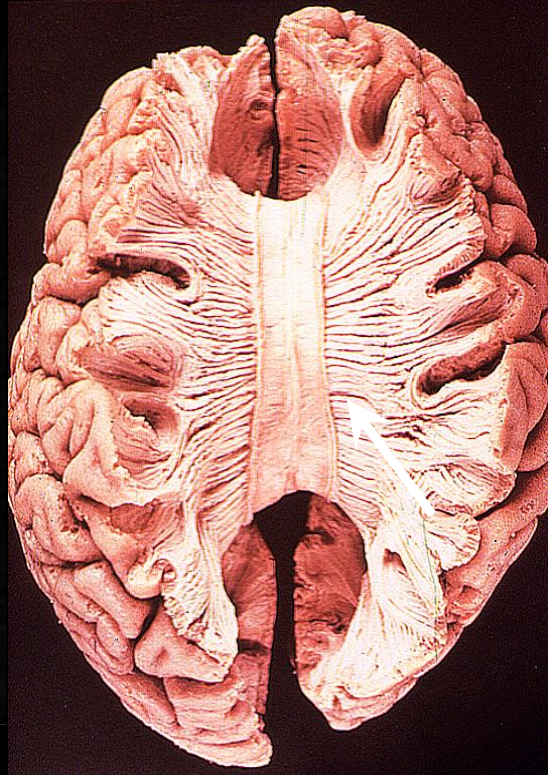
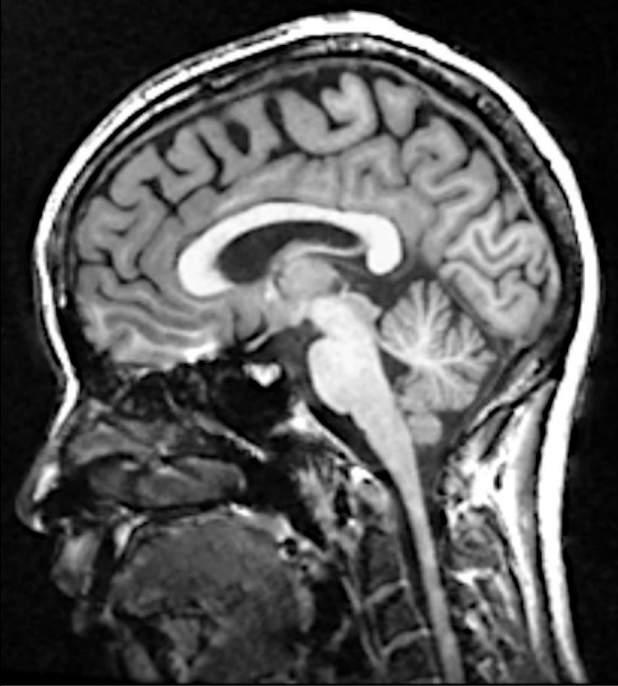


Fat-tailed dunnart





The corpus callosum connects the two brain hemispheres



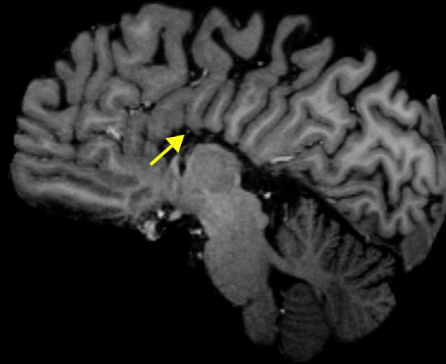


# Corpus Callosum Dysgenesis – Brain wiring variations

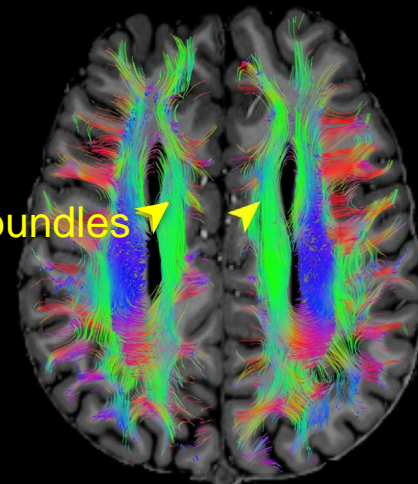
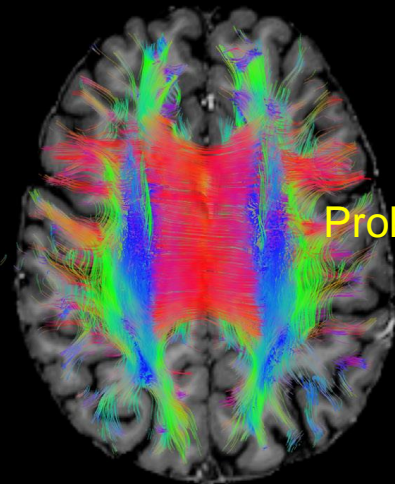
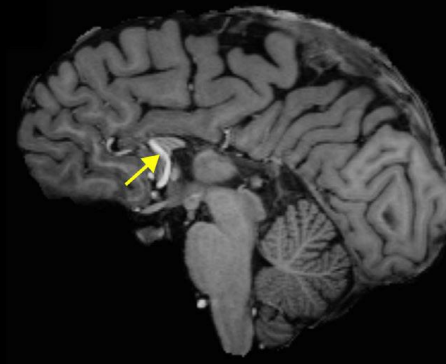
Neurotypical CC



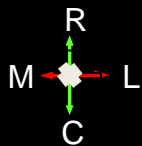
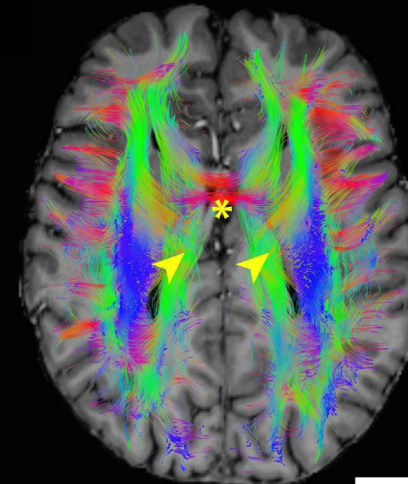
Complete CCD



Partial CCD

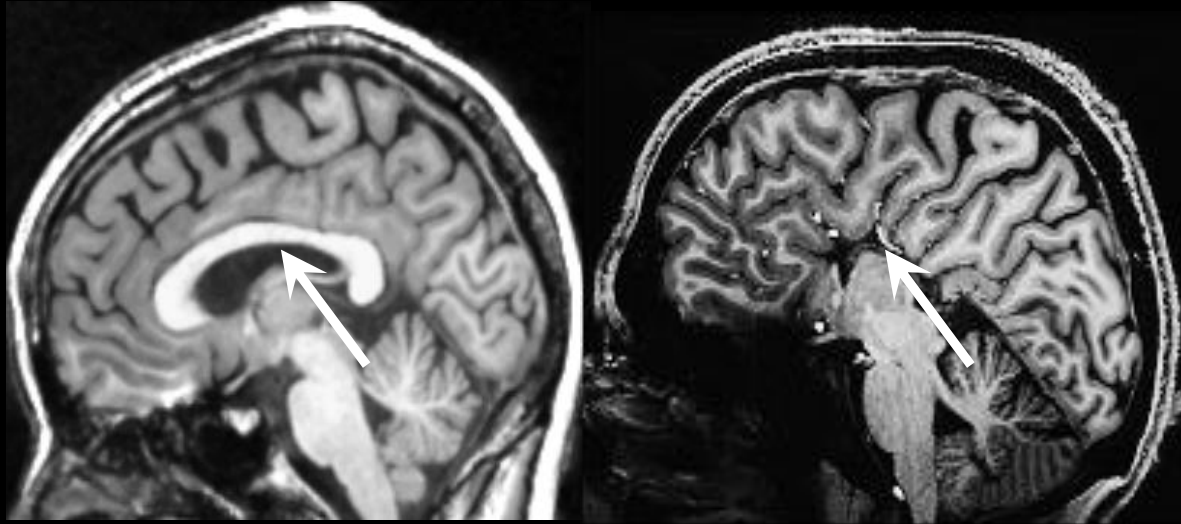


Probst bundles

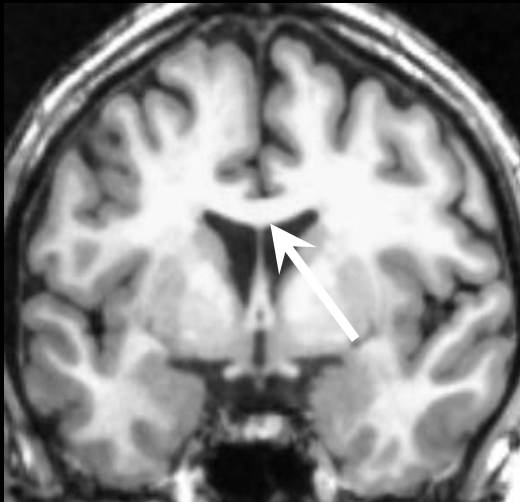




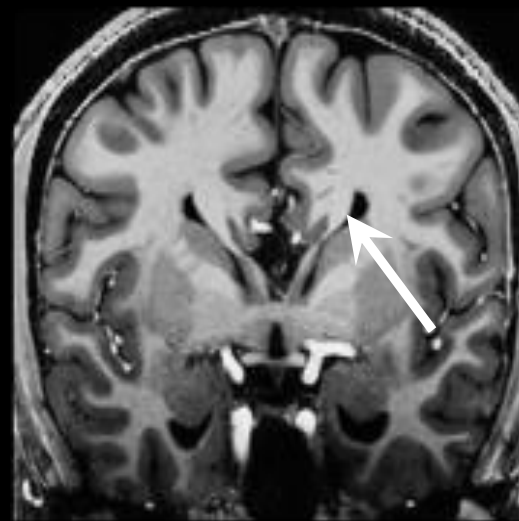
# Complete Corpus Callosum Dysgenesis/Agenesis is caused by a defect in glial cells



Dr Ilan Gobius



Neurotypical Control



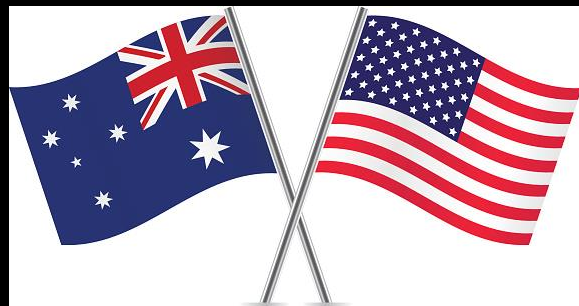
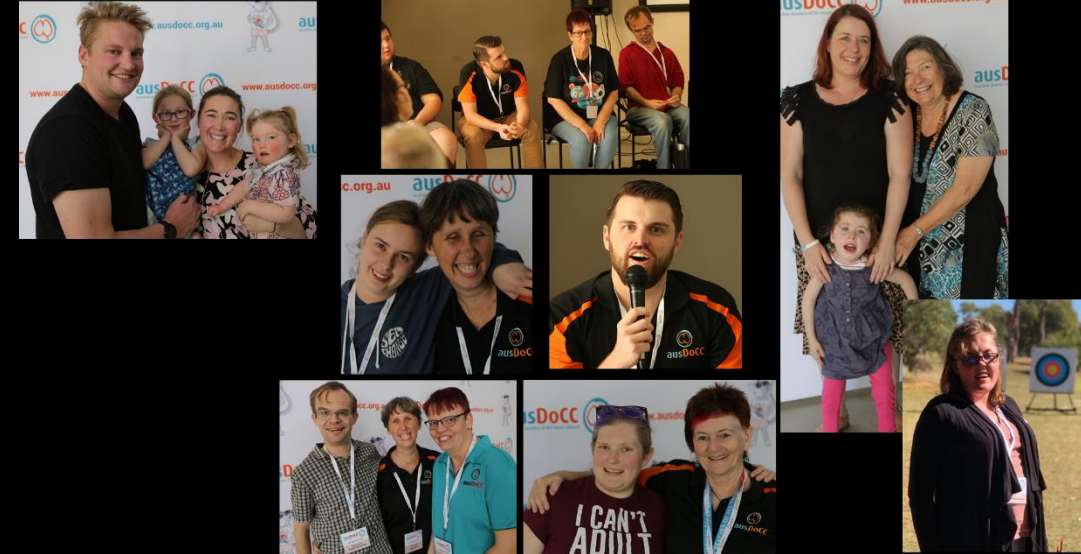
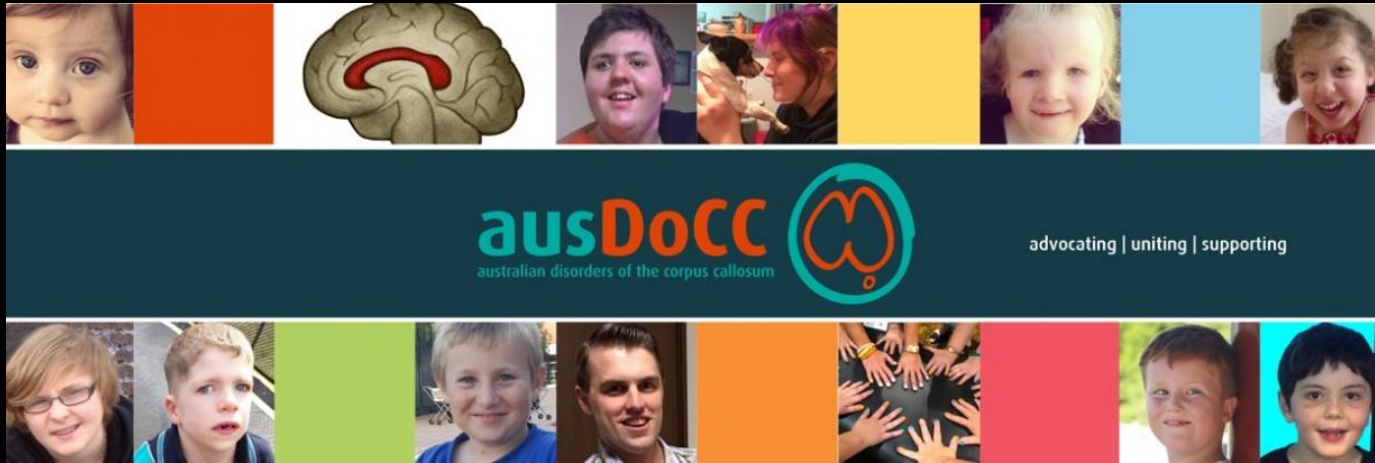
Corpus Callosum Dysgenesis



Dr Laura Morcom



# How do disorders of the corpus callosum affect people?



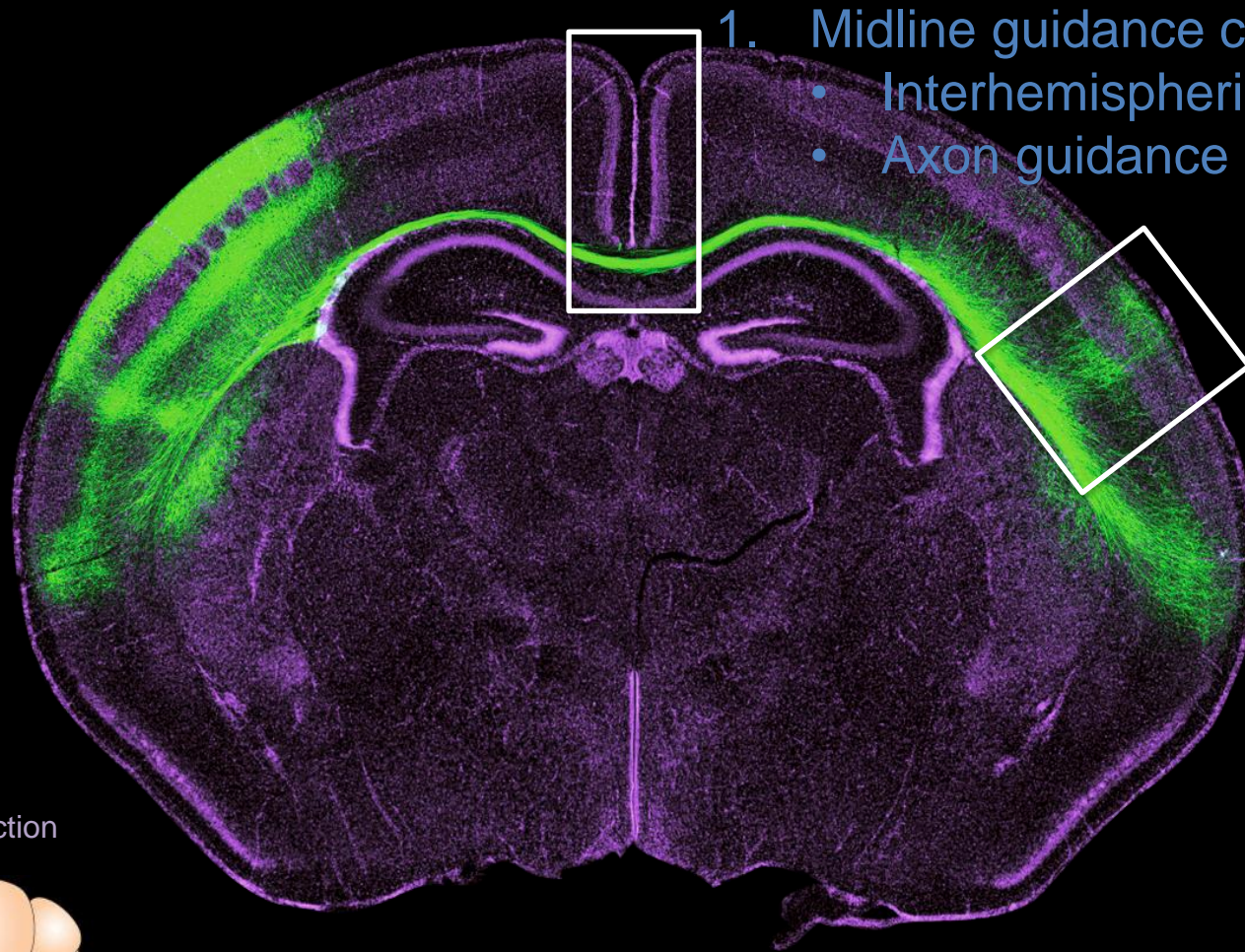
# What mechanisms control the wiring?



Mouse



Fat-tailed dunnart



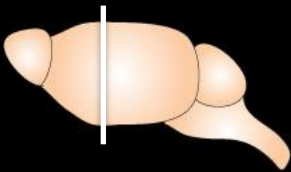
## 1. Midline guidance cues

- Interhemispheric remodeling by specialized glia
- Axon guidance molecules and receptors

## 2. Contralateral guidance cues

- Molecular gradients
- Activity patterns

coronal section

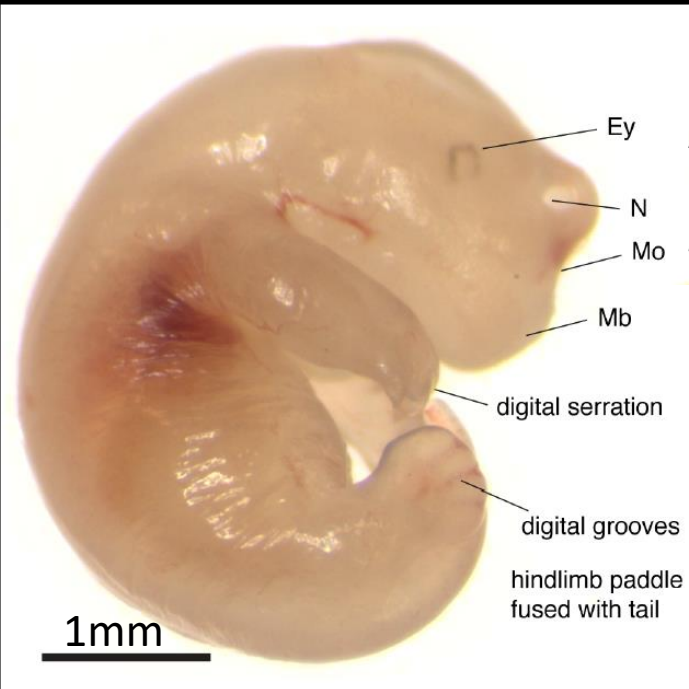


P10 Mouse corpus callosum electroporated with eYFP at E15.5

# The fat-tailed dunnart (*Sminthopsis crassicaudata*)



Adult dunnart  
Av. Body length 60-90 mm



Dunnart birth

P0

18

19

20

21

22

23

24

25

26

27

28

29

Stage equivalent

E10

E11

E12

E13

E14

E15

E16

E17

E18

Mouse embryonic / postnatal day equivalent

P0-P4

Mouse birth

P4-P10

P10+

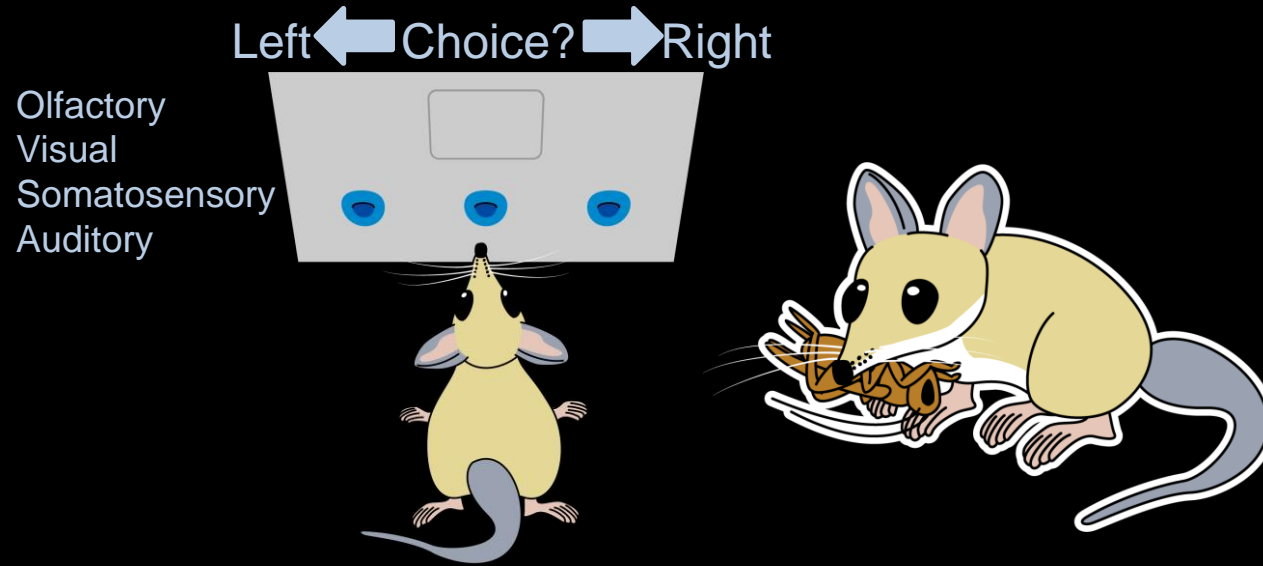
P41-50: Ear canals open  
P51-70: Eyes open  
↓  
P51+

P40

P51+

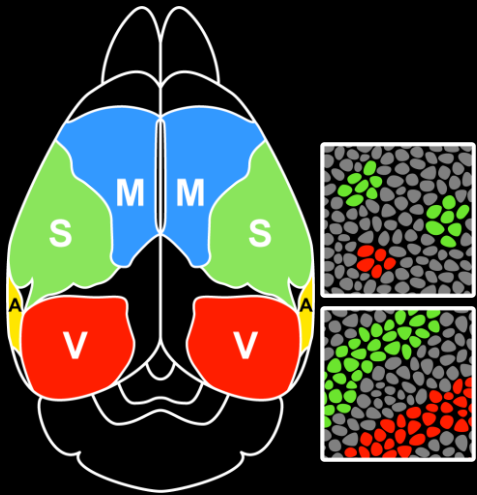
5mm

# Are early activity patterns critical for later brain function?



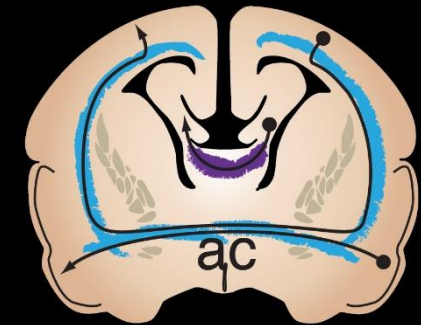
Behavioral assays in dunnarts

- Sensory decision-making tasks
- Prey capture – decision-making and prediction



Perturb the system during development

## FUNCTION AND BEHAVIOR



Examine circuit anatomy

# Neurodegeneration & neuroimmunology

