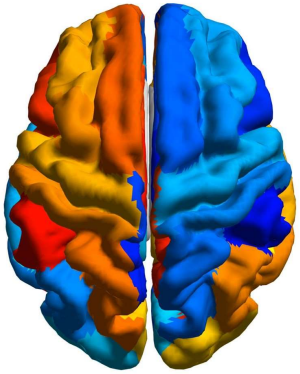
Genetics of human brain asymmetry



Clyde Francks
Professor of Brain Imaging Genomics
Max Planck Institute & Radboud University Medical Center, Nijmegen
March 2023

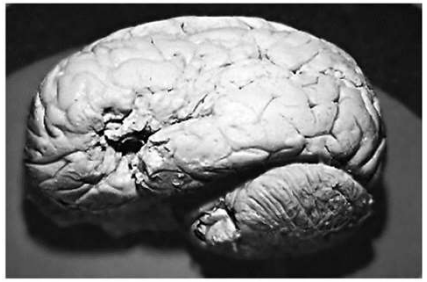
MAX-PLANCK-GESELLSCHAFT
Donders Institute for Brain, Cognition and Behaviour
Radboudumc

Slide 1

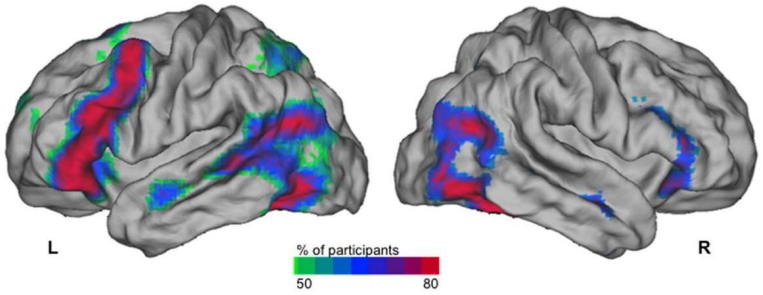
1 As part of the overall / general / clinical WG presentations, we will ask presenters to include 1 summary slide at the top of their slide deck that we can share publicly outside of ENIGMA. Here is a template slide deck which you definitely don't have to use, but we have added some example info here that your summary slide could include. Other presentations do not need to include this slide.

Sophia Thomopoulos; 19-05-21

Human brain asymmetry



"... it would follow that the two halves of the brain do not have the same attributes..." – *Paul Broca, 1863*

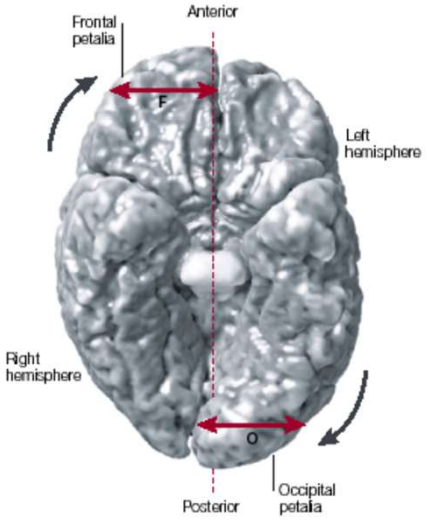


Covert sentence generation versus word list recitation (144 right-handers)

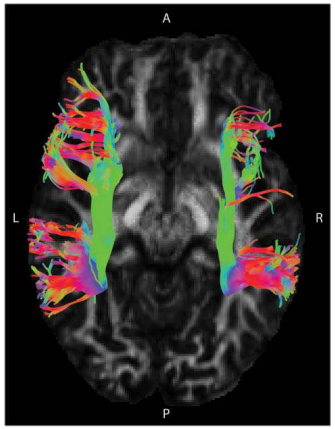
Mazoyer *et al*. 2014:

- Many functions asymmetrical to a degree
  - E.g. related to language, spatial attention, hand motor control (90% right-handed)

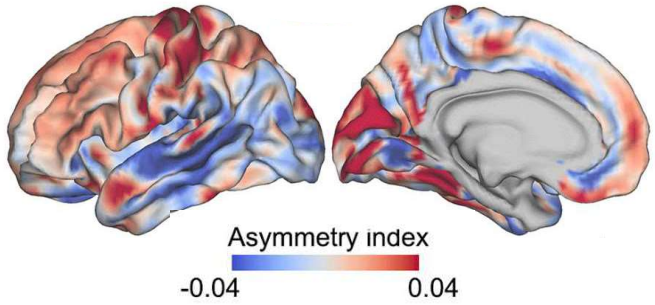
Hemispheric differences of brain structure



Brain 'torque'
Toga and Thompson,
Nat Rev Neurosci 2003



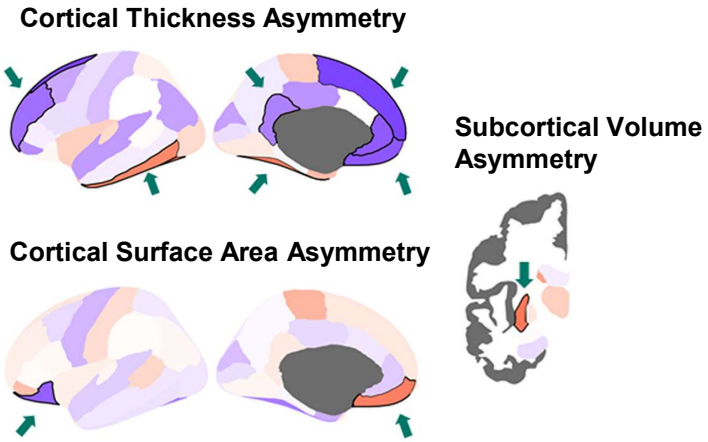
Arcuate fasciculus asymmetry
Ocklenburg et al. Rev Neurosci 2016



Mean cortical thickness asymmetry
vertex-wise in 31,864 individuals
Sha et al. PNAS 2021

MAX PLANCK

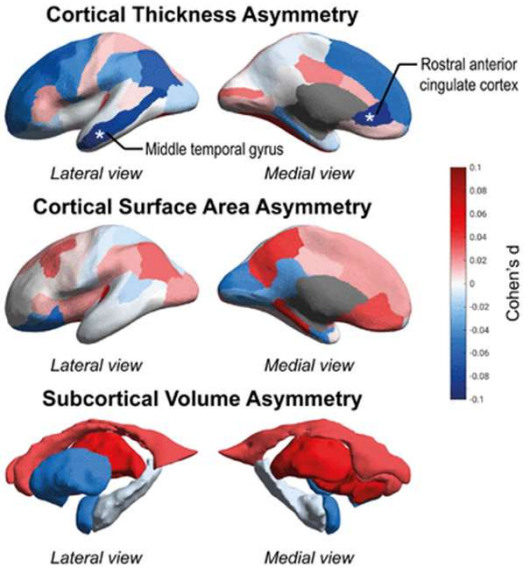
Brain structural asymmetry in psychiatric traits



Autism

1,774 affected, 1,809 controls, 54 datasets

Postema et al. Nat Comm 2019



Schizophrenia

5,080 affected, 6,015 controls, 46 datasets

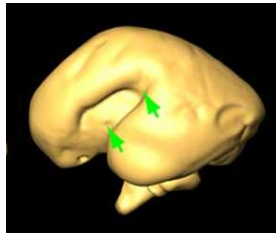
Schijven et al. PNAS, in press

- Largest studies of brain asymmetry in autism and schizophrenia to date
- Altered development of asymmetry may sometimes be part of disorder etiology

Early development of human brain and behavioural asymmetry

- 10 weeks gestation: 85% human fetuses move right arms more than left
- 15 weeks gestation: Thumb sucking predictive of handedness aged 12 years

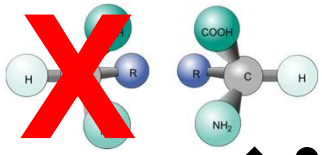
- Middle gestation and onwards: Structural lateralization of cerebral cortex (temporal lobe, perisylvian regions)

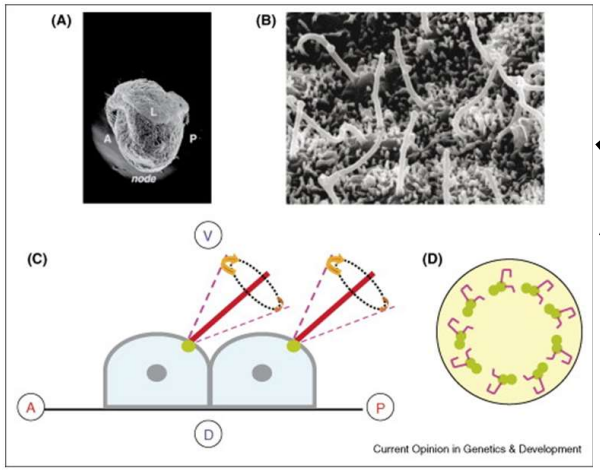


- Early developmental origin indicates genetic basis of brain asymmetry

Hepper et al. 1998; 2005: Hering-Hanit et al. 2001

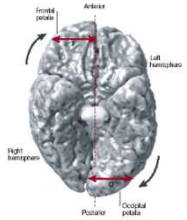
How to create a left-right axis

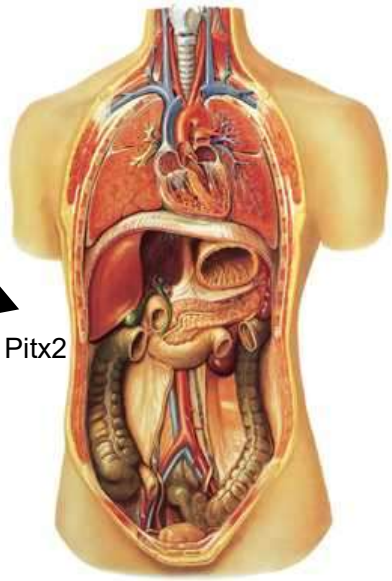




Takaoka et al., Curr Opin Gen Dev 2007

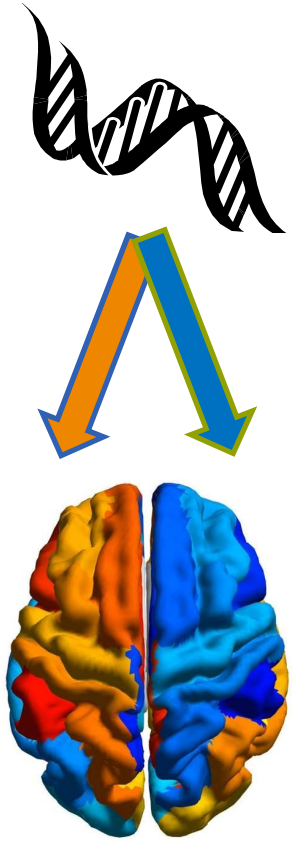
?





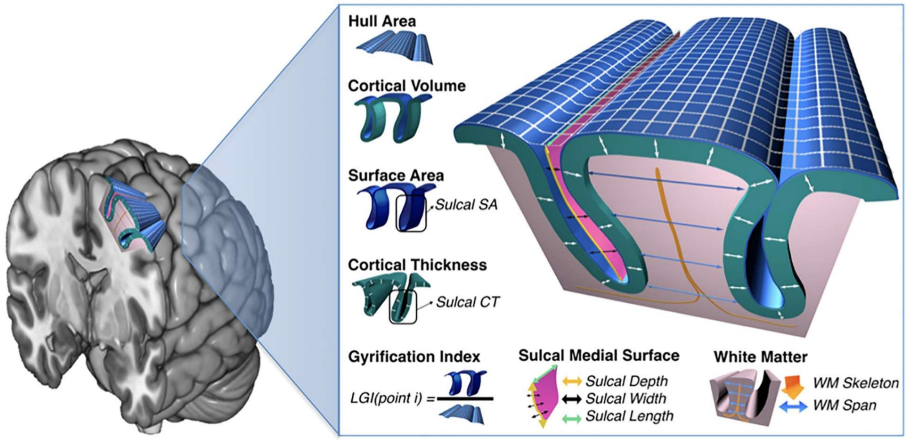
Nodal, Lefty2, Pitx2

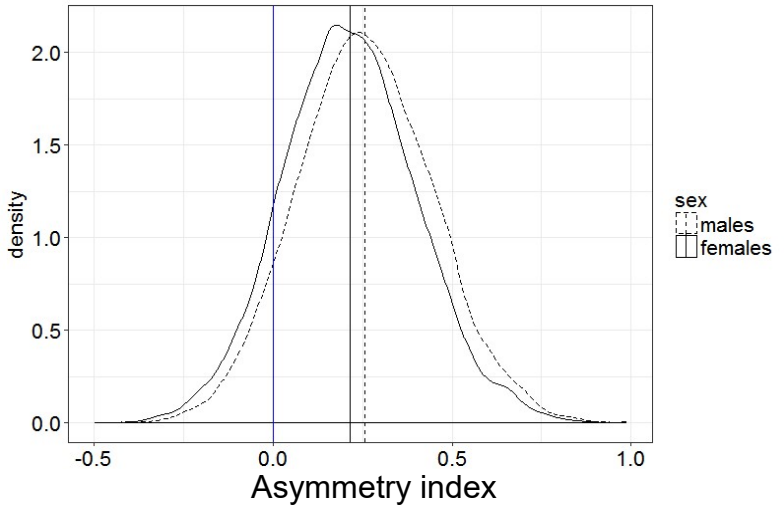
Genetics of brain asymmetry



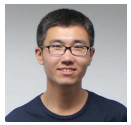
- How does the brain become asymmetric in development?
  - Not obviously linked to left-right axis of visceral organs
  - People with *situs inversus* of the viscera have **roughly normal rates** of left-handedness and left-hemisphere language dominance
- Which genes are involved - and when during the lifespan?
  - Clues to pathways and mechanisms
  - Hard-wired versus plastic aspects of asymmetry
  - Genetic overlaps with psychiatric/neurological traits can suggest shared mechanisms

Imaging genetics of brain structural asymmetry in >32,000 adults (UK Biobank)





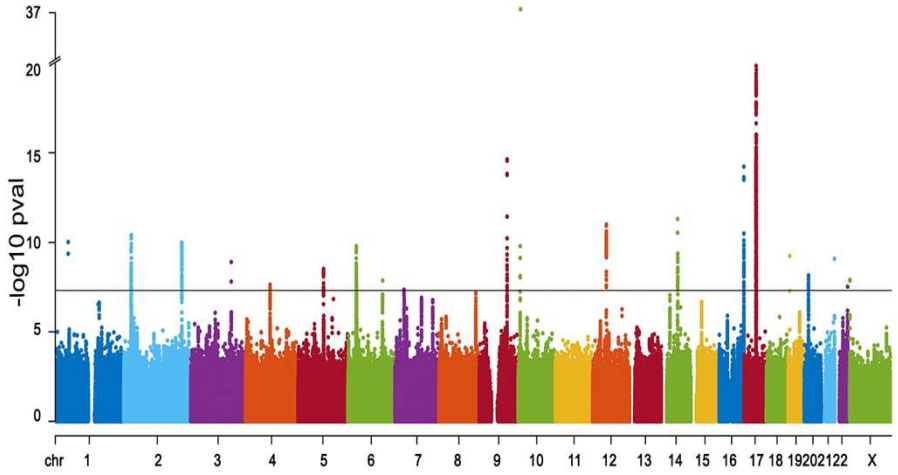
- Freesurfer automated cortical parcellation and subcortical volume measurement
- Left and right homologous regional measures
- Asymmetry index for each individual and region (L-R)/((L+R)/2)

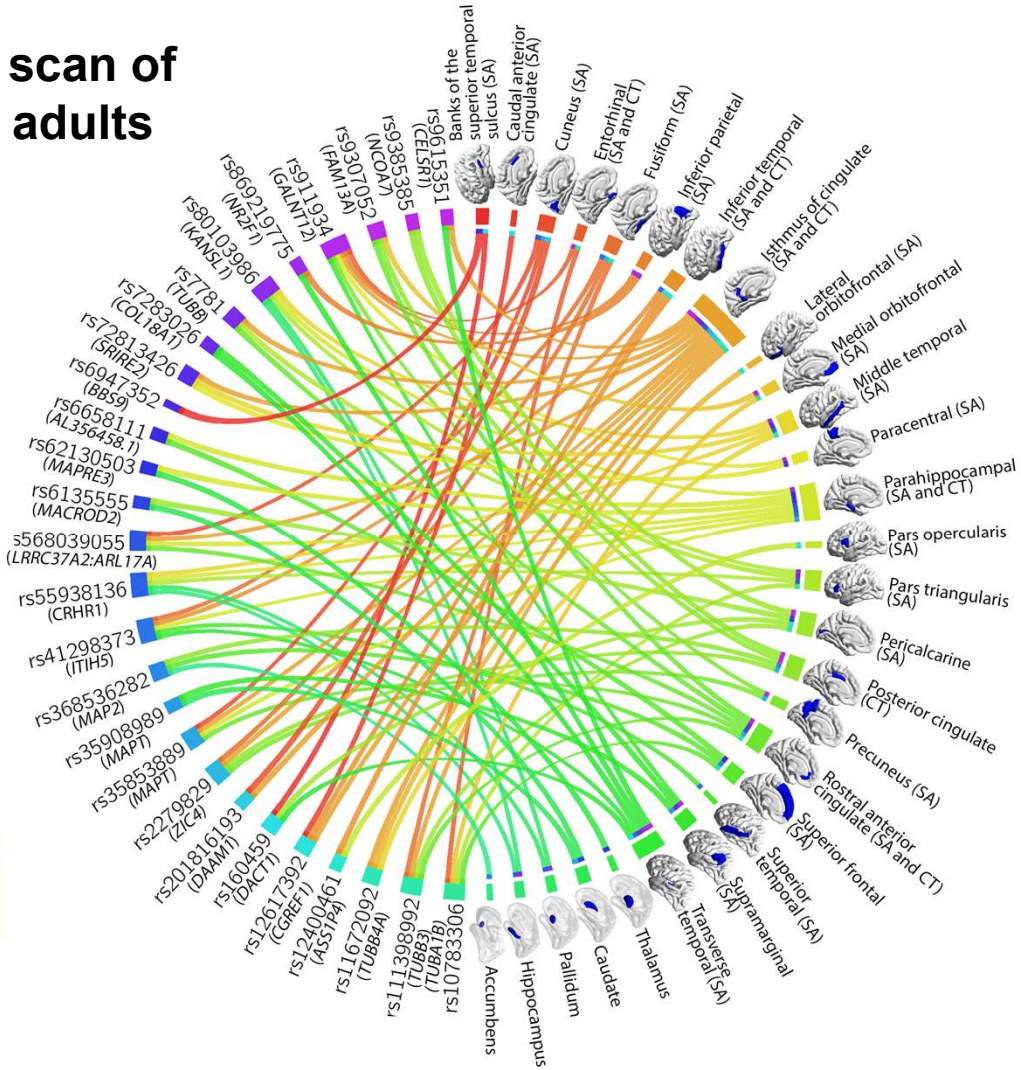


Sha et al. Nature Human Behaviour 2021

Multivariate genome-wide association scan of regional brain asymmetries in >32,000 adults

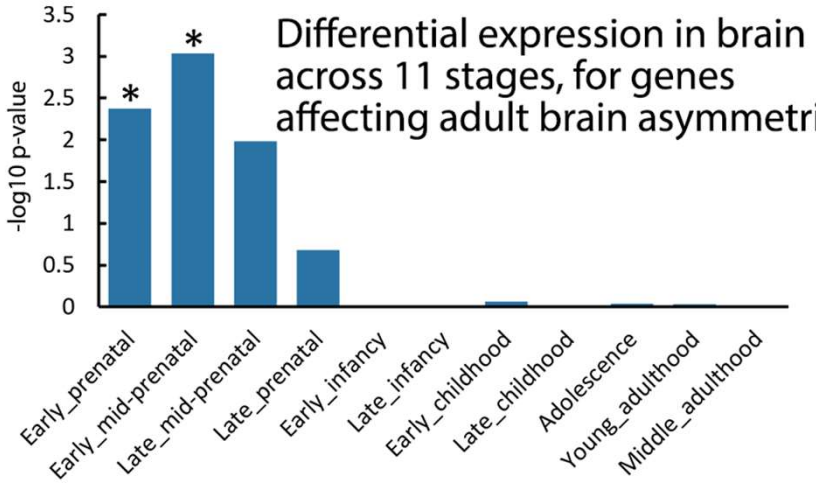
- 21 genomic loci where SNPs are significantly associated with variation in adult brain structural asymmetry:

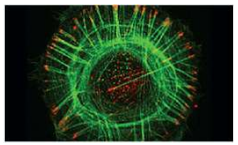




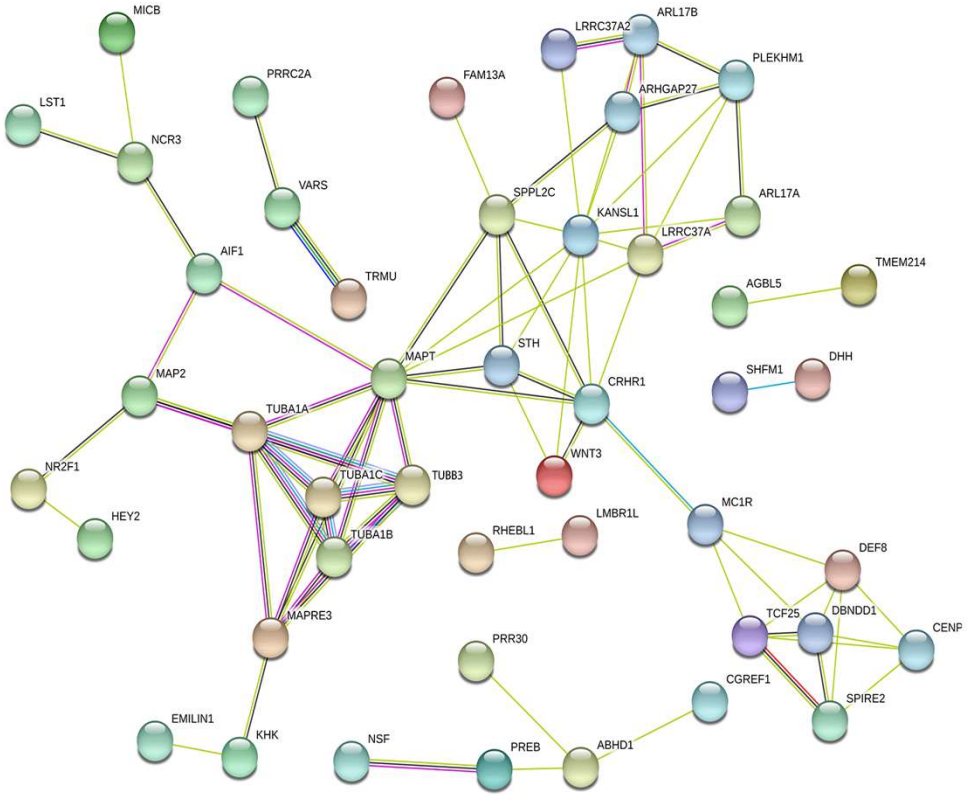
Sha et al. Nat Hum Behav 2021

Genes associated with variation in adult brain asymmetry



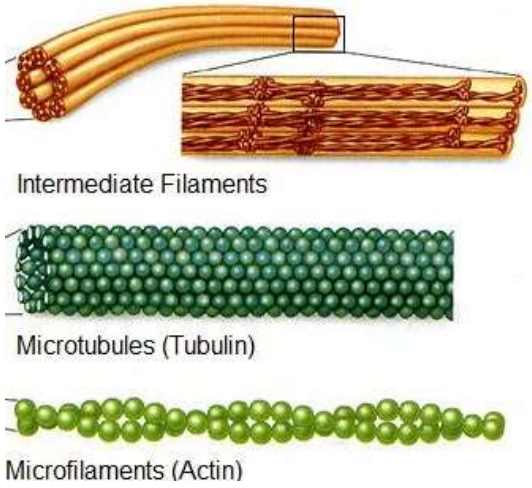


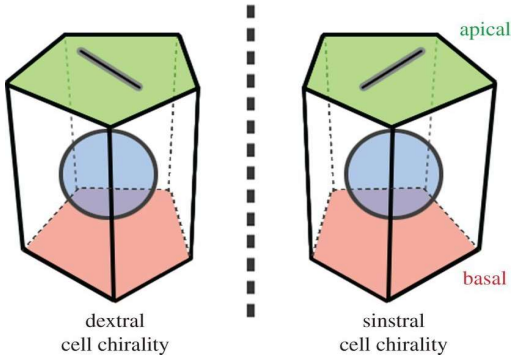
- Enrichment for microtubule-related functions
- Likely to affect the cytoskeleton (internal protein skeleton of cells) – controls cell shape, movement, internal transport, growth

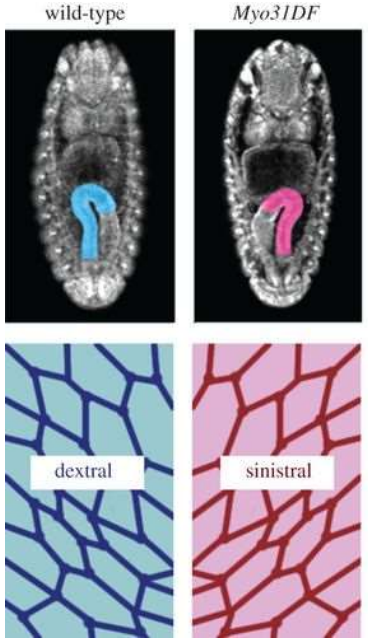


Sha et al. Nat Hum Behav 2021

Cellular chirality for L-R axis formation of the brain?







- Cytoskeleton plays a role in cellular chirality and left-right axis formation of Drosophila hindgut
- Organ-intrinsic, i.e. not depending on signalling from elsewhere
- Related mechanisms in snail and frog embryos

Inaki et al. 2016 https://doi.org/10.1098/rstb.2015.0403

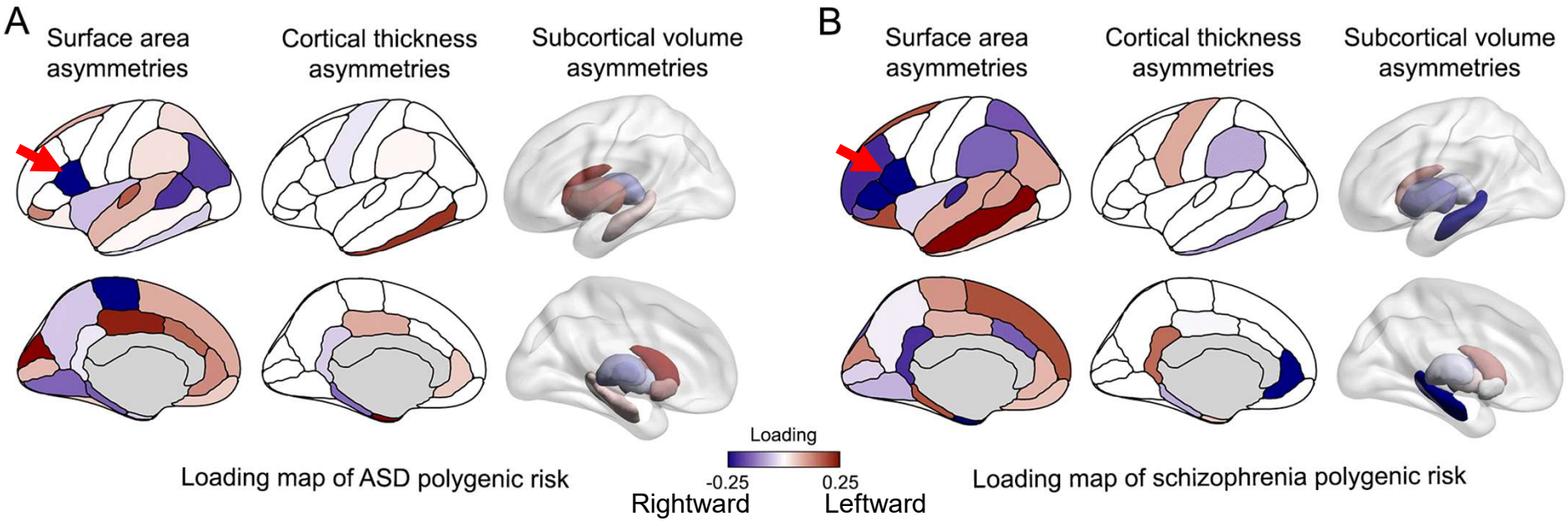
New research line: Neurogenetics of brain asymmetry in mice

Danielle Houwing

- Neurophysiological and molecular asymmetries reported in mice:
  - Auditory cortex, hippocampus
- Study the mouse as a model for brain asymmetry and its genetic contributions
  - Knockout lines for genes implicated by human work (first TUBB3, AGBL5)
  - Spatially resolved transcriptomics in brain tissue, immunohistochemistry, MRI
- Can mice be used to study embryonic development of mammalian brain asymmetry?
  - Hypothesis: Cellular chirality during formation of the neural tube

Disorder polygenic risks and brain asymmetry

(32,256 UK Biobank participants)



- Autism and schizophrenia polygenic risks showed significant multivariate associations with brain asymmetry (ASD $r=0.03$, $p=2.17\times10^{-9}$; schizophrenia $r=0.04$, $p=2.61\times10^{-11}$)
- Neither polygenic risk was associated with more male-like or female-like average brain asymmetry

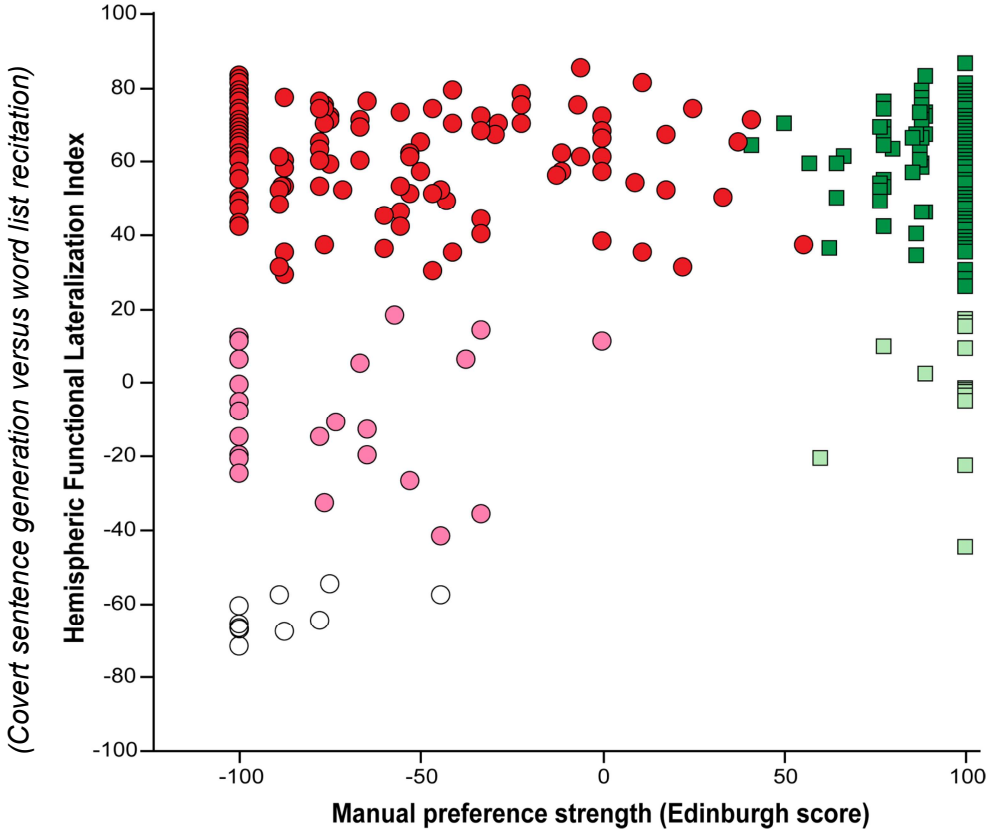
Sha *et al.* Mol Psychiat 2021

Handedness

- Roughly 90% of people right-handed
- Increased rates of non-right-handedness (roughly 2x) in meta-analysis studies of:
  - Autism
  - Schizophrenia
  - Intellectual disability
- Suggests overlapping genetic and developmental contributions to altered brain asymmetry and psychiatric conditions
  - The large majority of left-handed people do not have these conditions

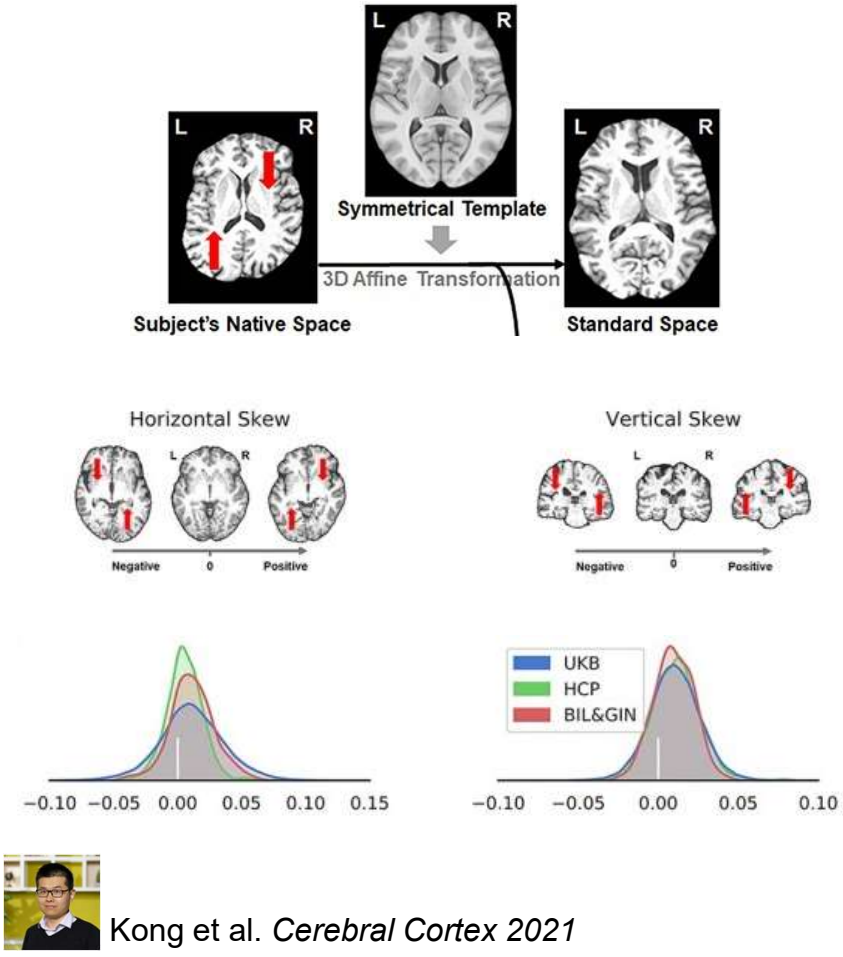
Papadatou-Pastou & Tomprou 2015; Markou et al. 2017; Hirnstein & Hugdahl. 2014

Handedness and hemispheric language dominance



- 297 healthy adults, balanced for handedness (Mazoyer et al. 2014)
- Handedness only weakly related to hemispheric language dominance
- Handedness a poor predictor of post-stroke aphasia recovery (review by Watila & Balarabe 2015)

Brain torque and handedness

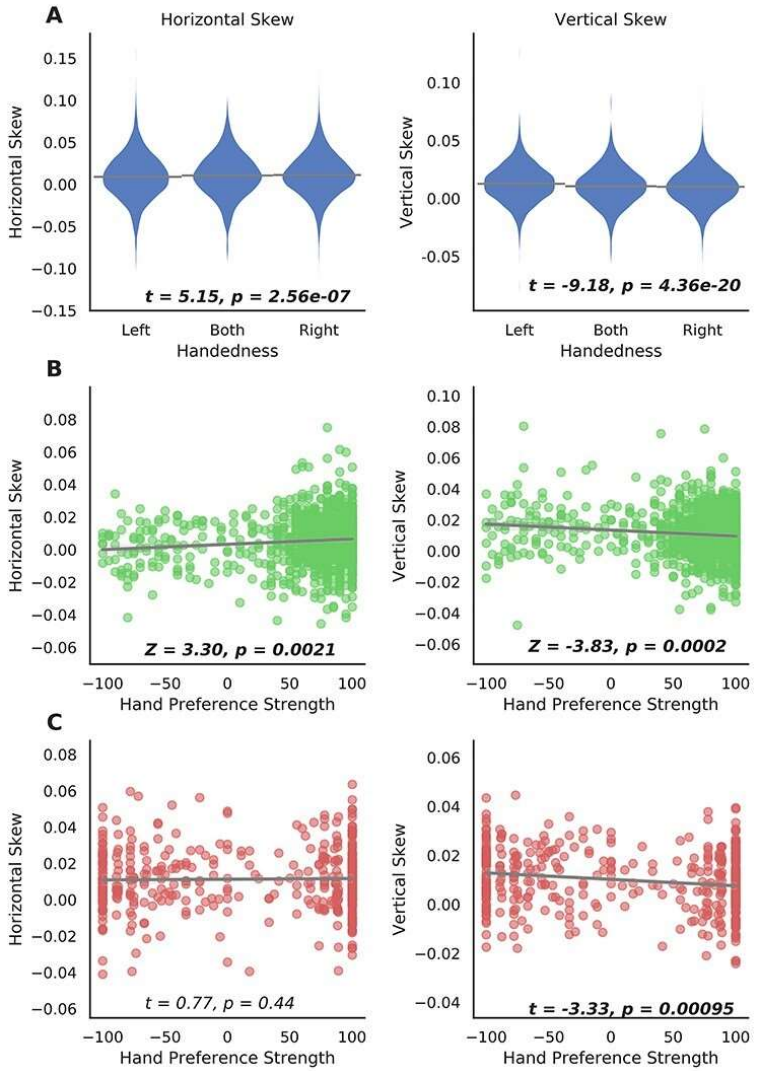


Kong et al. *Cerebral Cortex 2021*

UK biobank

HCP

BIL&GIN

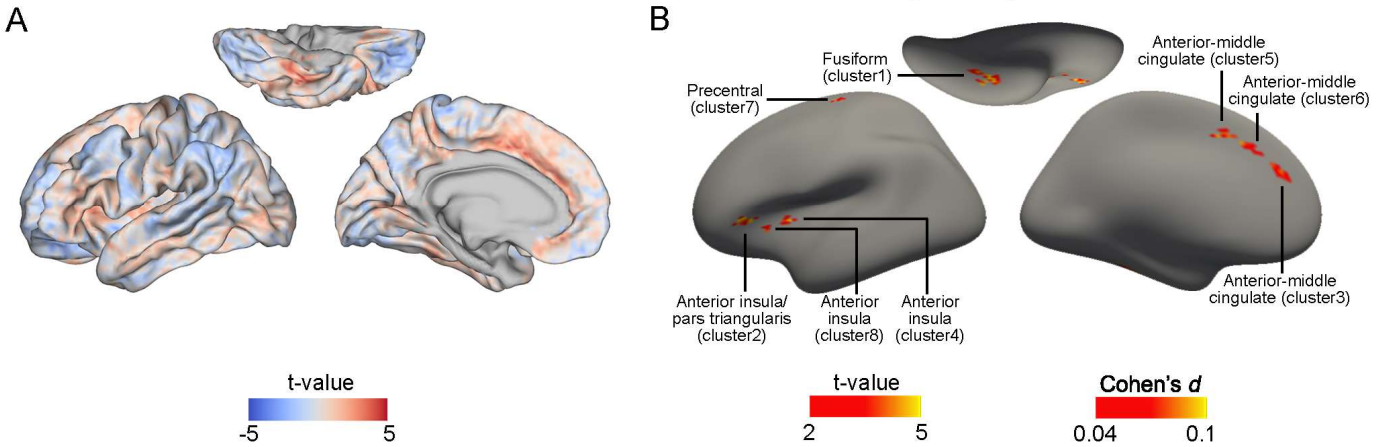


Handedness & cortical asymmetry

28,802 right-handers vs 3,062 left-handers
UK Biobank

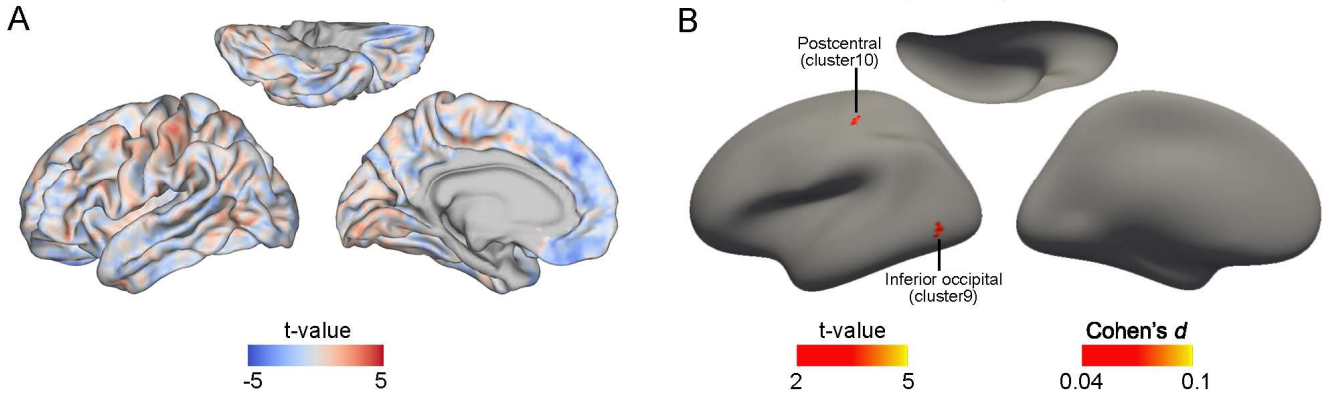
- Inter-hemispheric co-registration to map asymmetry at high resolution
- Ten clusters showed rightward shift of asymmetry in left-handers
- Indicates increased neural resources in right hemisphere for left hand control

Handedness-associated surface area asymmetry



Vertex-wise p<0 .001; cluster-wise p<0.05 (random field)

Handedness-associated cortical thickness asymmetry



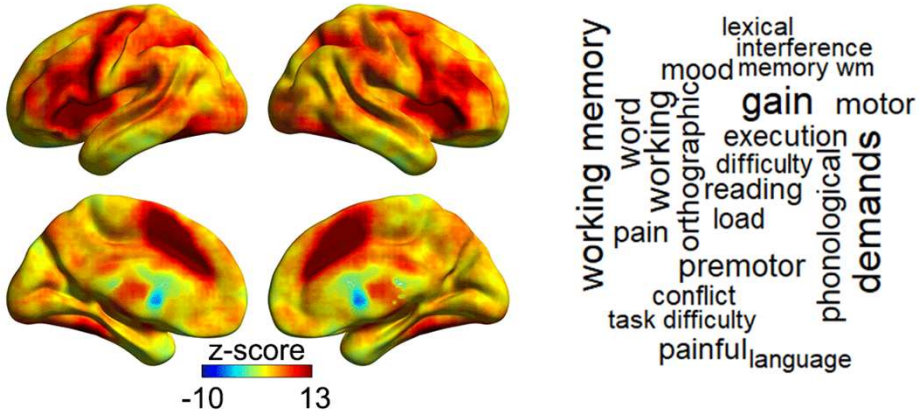
Sha et al. PNAS 2021

Functional annotation of handedness-associated cortical regions

Co-activation maps and functions based on meta-analyzed fMRI data from 14,371 studies (Neurosynth database)

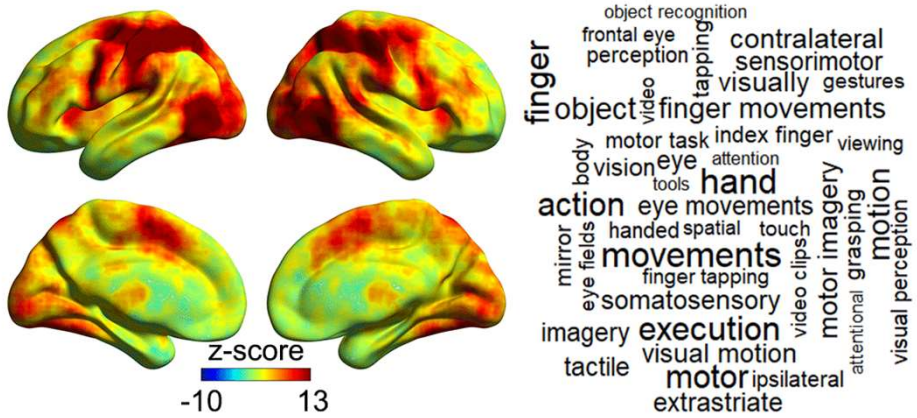
A

fMRI-based functional annotation of regions showing associations of their surface area asymmetries with hand preference



Language-related regions
Including inferior frontal cortex

fMRI-based functional annotation of regions showing associations of their cortical thickness asymmetries with hand preference



Primary somatosensory cortex
Visual cortex

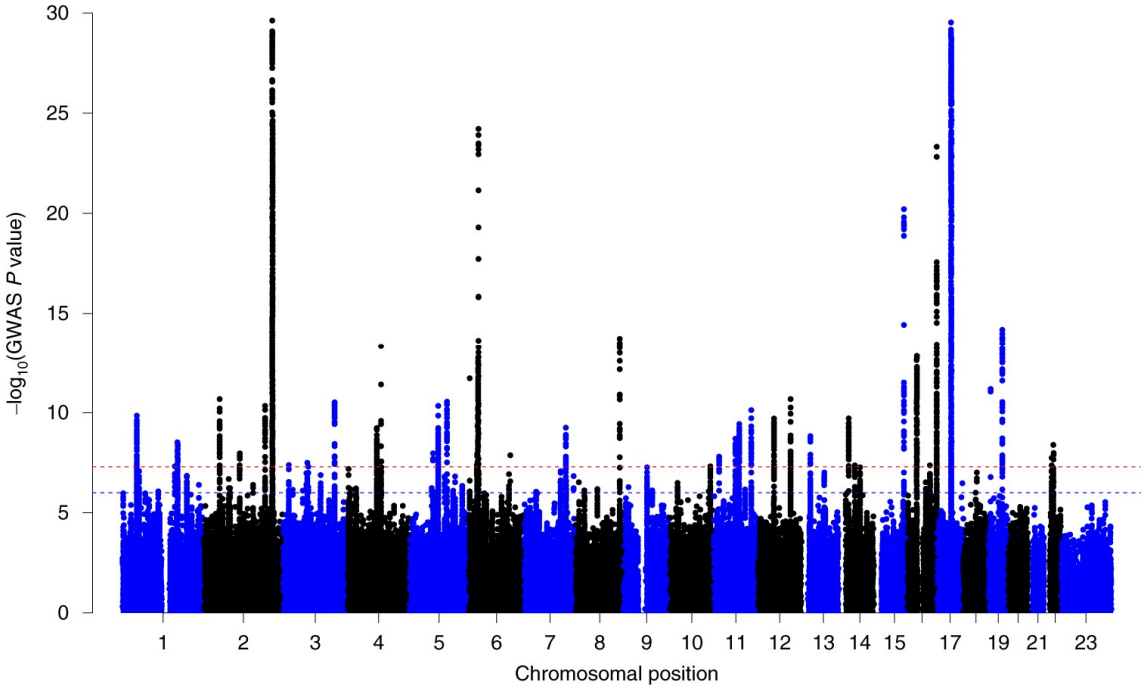
Sha et al. PNAS 2021

Genome-wide association scan for left-handedness

- 194,198 left-handed
- 1,534,836 right-handed

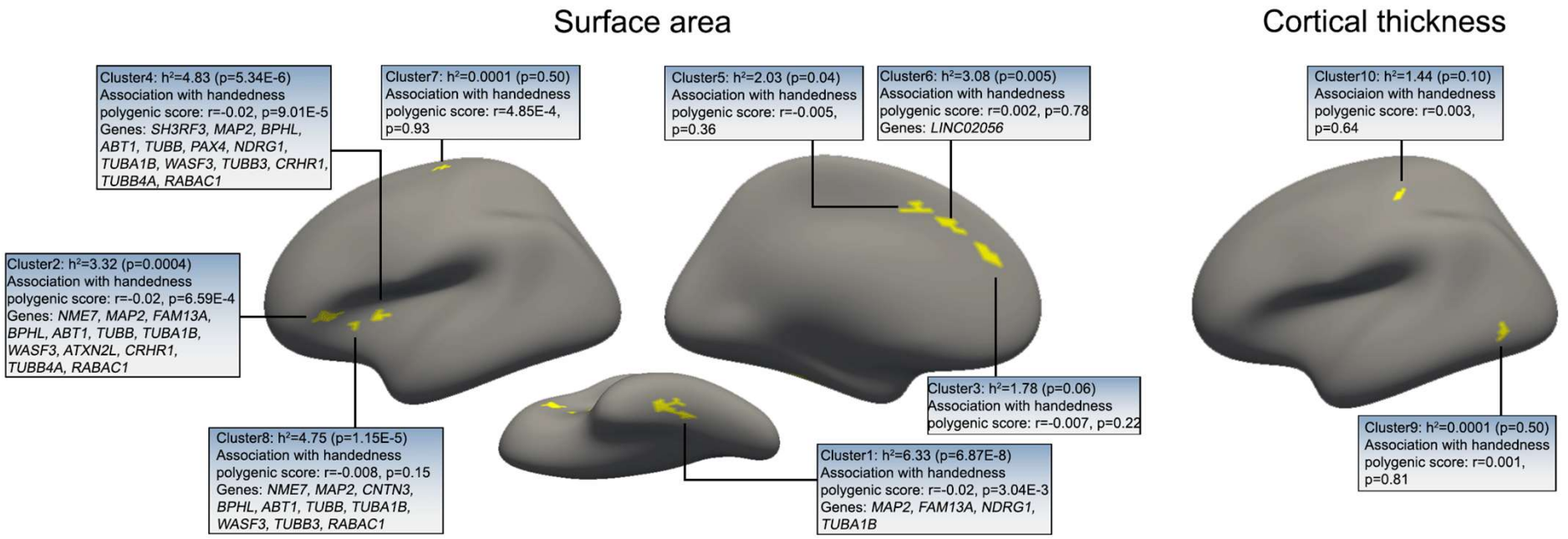
- 48 common genetic variants associated with left-handedness

- We queried these variants in the UK Biobank genetic & brain image data...



Cuellar Partida et al. 2020

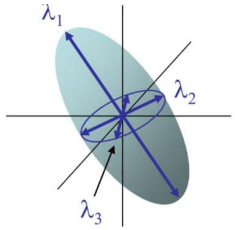
Genetic contributions to handedness-associated cortical asymmetries



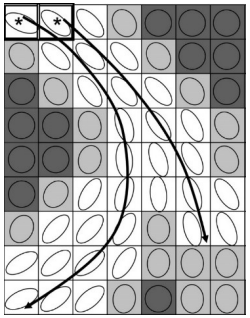
- Surface area asymmetries of language-related regions were heritable and linked with handedness-associated loci
  - *Handedness and language share genetic/developmental/evolutionary links?*
- Thickness asymmetry of primary sensorimotor cortex was not heritable
  - *Downstream consequence of hand preference after establishment in early development?*

Sha et al. PNAS 2021

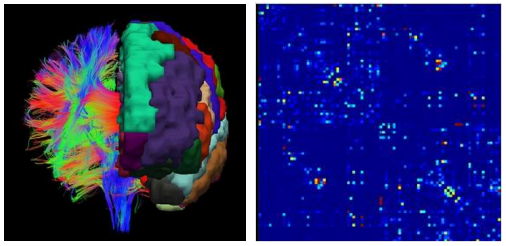
Genetics of white matter connectivity in 30,810 individuals



- Diffusion-weighted brain MRI
- Water molecules diffuse primarily along axons rather than radially
  - Limited by cell membranes and myelin



- Nerve fiber tracking
- Calculate the principal eigenvector of diffusion in each voxel
- Link neighbouring voxels with the same/similar principal orientation to construct ***streamlines***

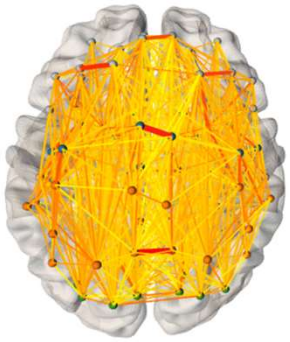


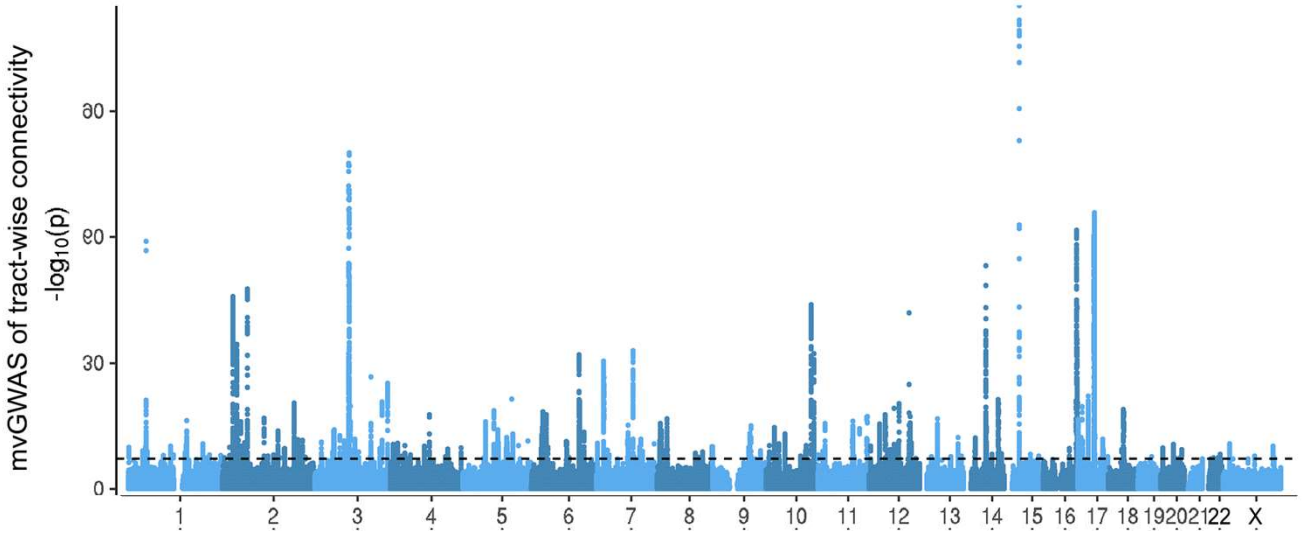
- Map 90 regional parcellations (automated anatomical labelling atlas) onto fiber tracking results
- **Connectivity matrix for each participant**:
  - Number of streamlines linking each pair of regions (weighted by regional volumes)

Sha *et al.* Science Advances 2023

Images from Mori et al. Ann Neurol. 1999. Mori et al., Neuron 2006. Schiffler, Front Hum Neurosci 2017

Multivariate genome-wide association analysis of white matter connectivity in 30,810 participants

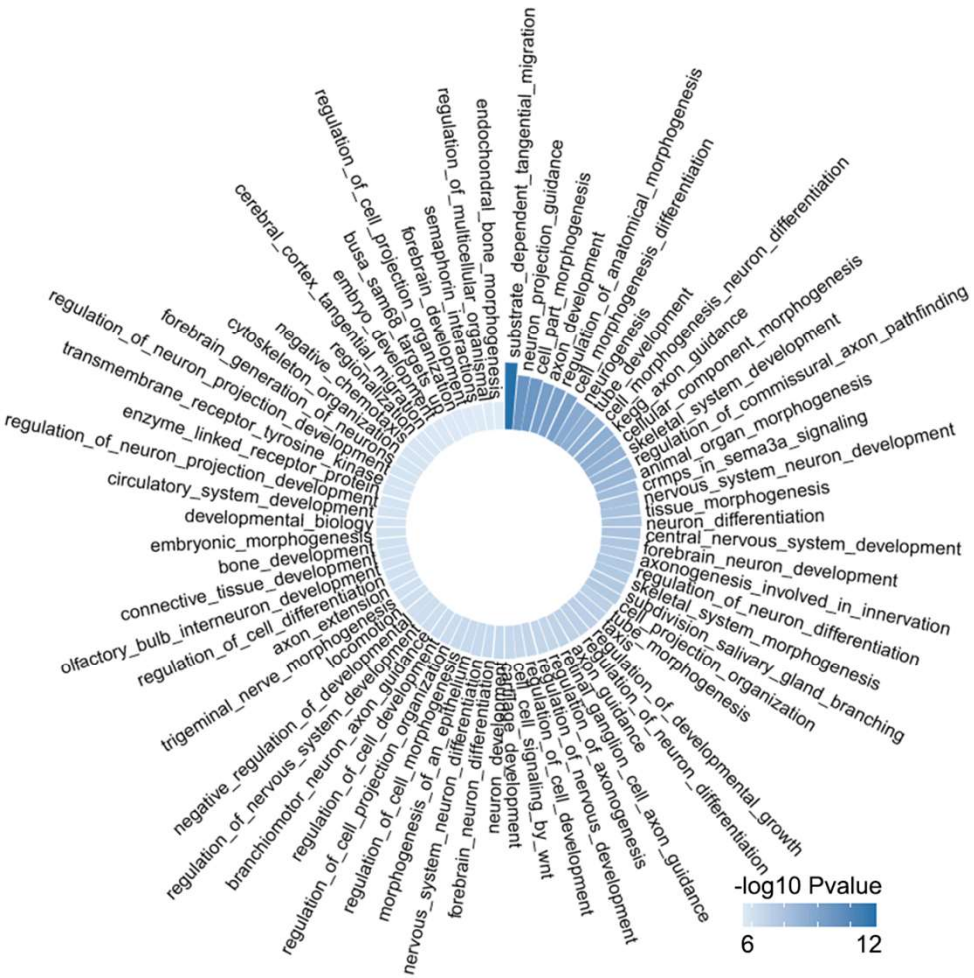


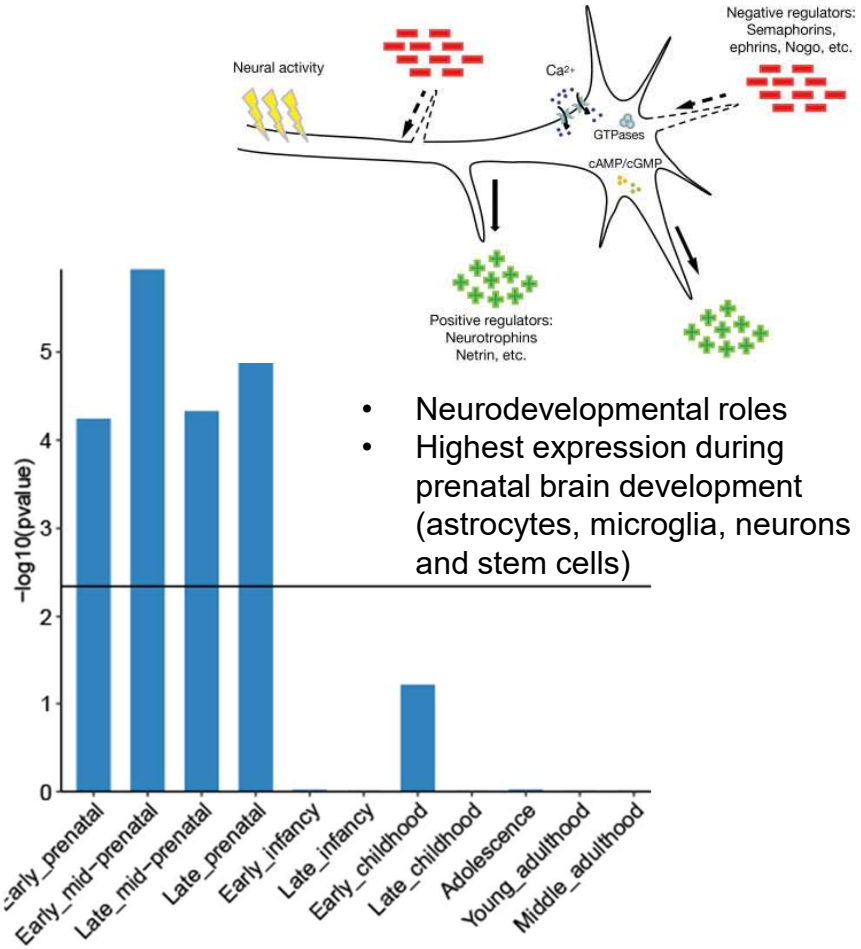


- Test each SNP simultaneously for its association across 851 white matter measures
- 181 genomic regions where single nucleotide polymorphisms SNPs are significantly associated with white matter connectivity

Sha *et al.* Science Advances 2023

Genes associated with white matter connectivity

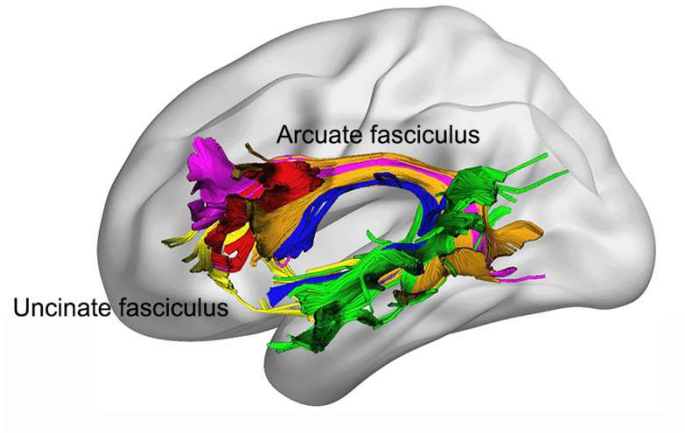




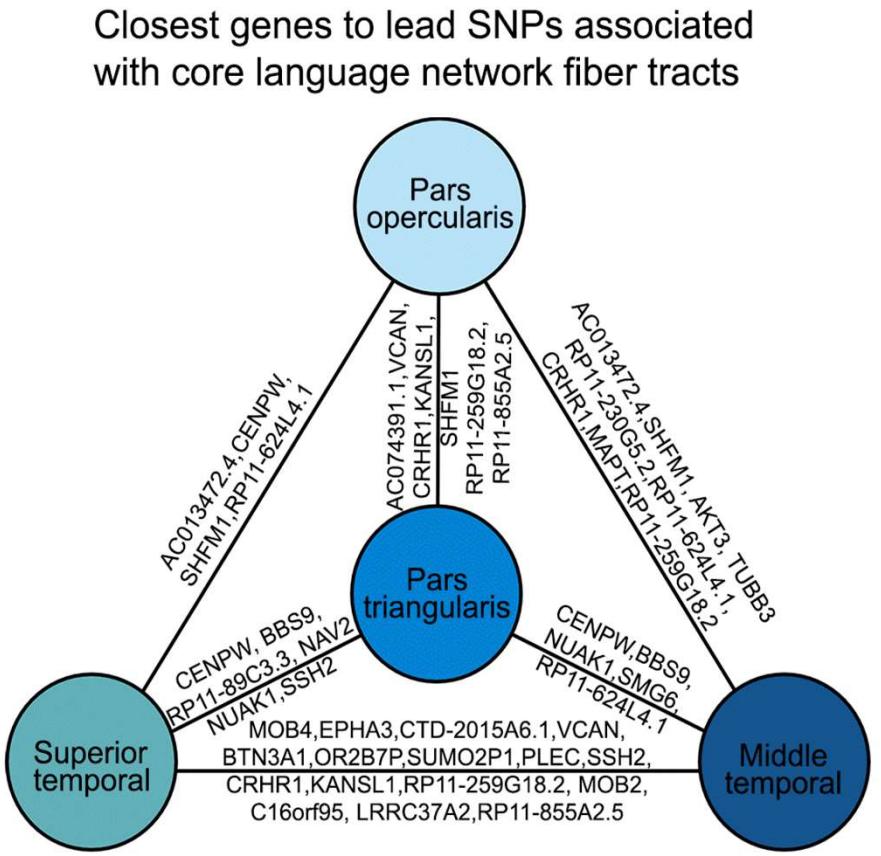
- Neurodevelopmental roles
- Highest expression during prenatal brain development (astrocytes, microglia, neurons and stem cells)

Sha *et al.* Science Advances 2023

Genetics of the left-hemisphere language network



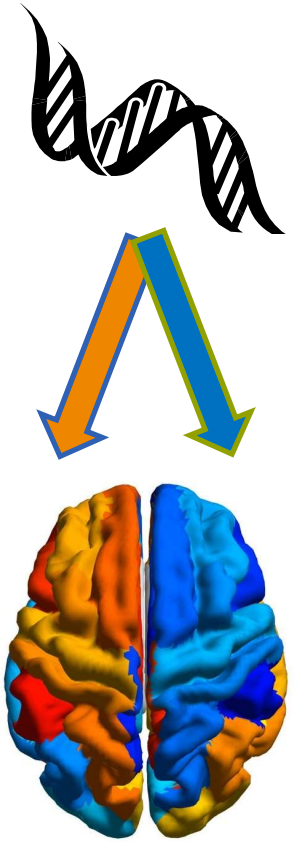
- Implicated genes include EPHA3
  - ephrin receptor subunit
  - regulates formation of axon projection maps
  - also associated with functional connectivity between language-related regions (Mekki et al. 2022)



Sha *et al.* Science Advances 2023

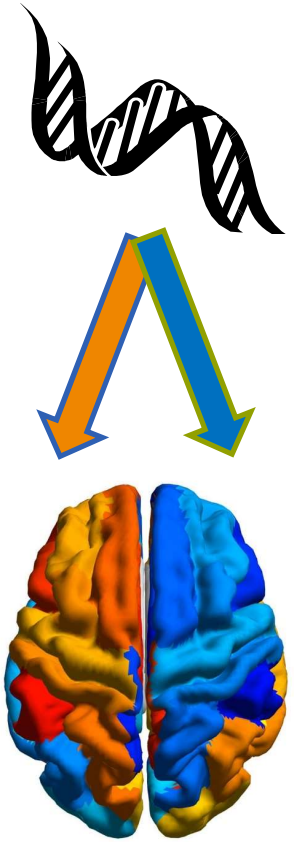
Summary of genetic association findings

- Large-scale studies have started to answer long-standing questions:
  - Which genes are associated with human brain asymmetry and/or the left hemisphere language network
  - Which regional asymmetries are associated with psychiatric traits, and how strongly
  - Gene-brain-behaviour/disorder associations
- Genes affecting adult brain structural asymmetry are especially active during embryonic brain development
- Microtubule involvement hints at a cellular chirality mechanism of brain L-R axis formation



Future directions

- Genetics of functional connectivity asymmetry
  - Large datasets limited to resting fMRI (not language task fMRI)
- Mouse as a model of asymmetrical brain development/structure/function
- Genetic overlap of brain asymmetry and brain disorders
  - Rare mutations affecting asymmetry and disorders?
- Higher resolution mapping of asymmetry changes in brain disorders
  - Including normative modelling (not necessarily simple group mean effects)



Thanks for your attention!

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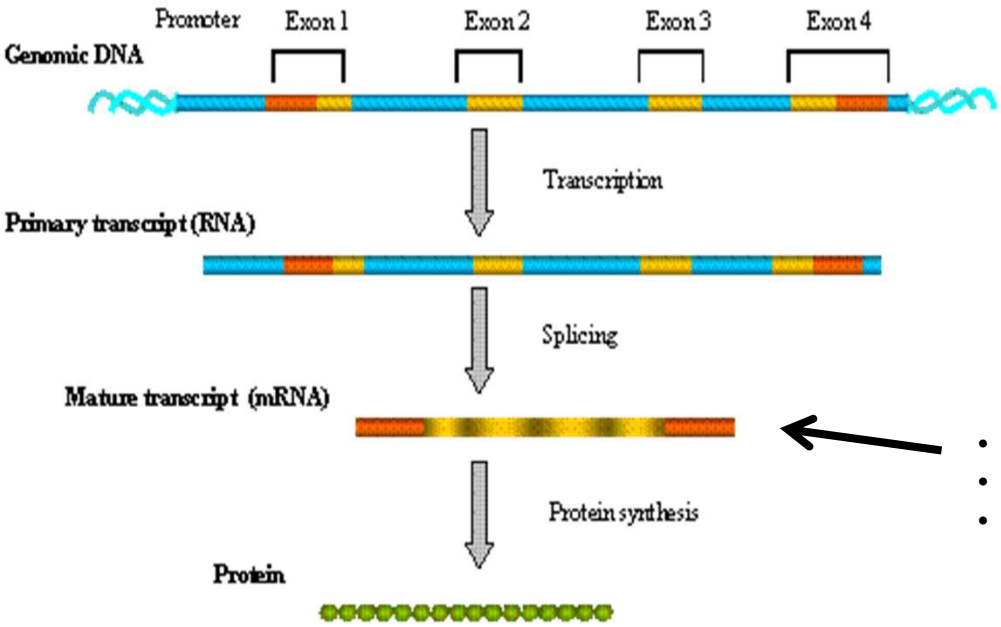
- Extra...

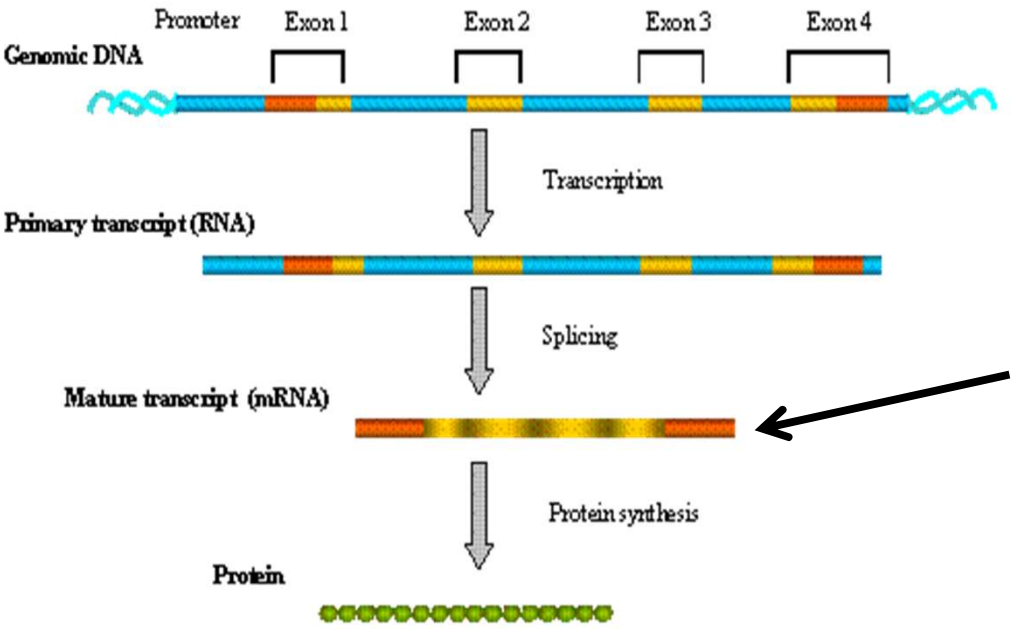
Genome to protein



- Millions of variants in the human genome that commonly differ between people
- Some alter protein structure and function
- Many affect the regulation of gene expression
- Heritability of individual differences

- Unstable molecule, continually replenished in living tissue
- Measure abundance in fresh/frozen post mortem samples
- Index of gene's activity in a given tissue and lifespan stage

Genome to protein

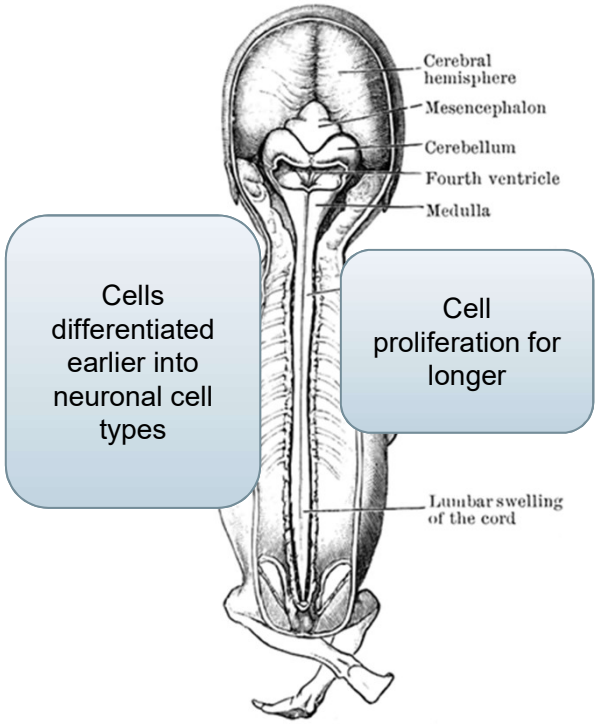


Studies have contrasted gene expression between left and right samples from human central nervous system

Asymmetry of maturation rates in spinal cord

- Increased right arm movement in human embryos 8 weeks post conception (Hepper et al. 1998)
- Before spinal-forebrain connections developed
  - Bottom-up development of brain asymmetry (hindbrain/spinal origin)?

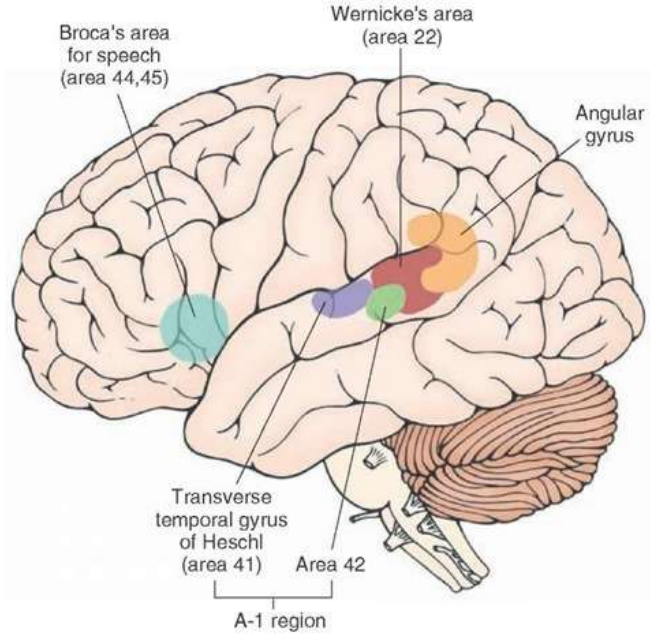
- Post mortem gene expression
  - Tissue bank: Human Developmental Biology Resource (UK)
  - 18 embryos, 4-8 weeks post conception
  - RNA sequencing: quantify expression of thousands of genes

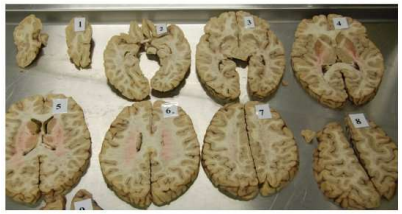


De Kovel et al. Biol Psych 2017

Asymmetry of adult auditory cortex

- Functional, neurophysiological, macro- and microanatomical asymmetry
- Left-sided neural oscillations tuned to syllabic speech rate? (Giraud & Poeppel 2015)
- Suggests lateralized activity of genes involved in neural electrophysiology, synapse transmission
- Contrast gene expression between left and right area 22
  - Human post mortem data, publicly available
  - Pletikos et al. Neuron (13 adult brains aged 18-55)
  - Hawlyrycz et al. 2011 (2 brains, more gene expression data per region)
  - Microarray transcriptomics mRNA quantified for approx. 14000 genes





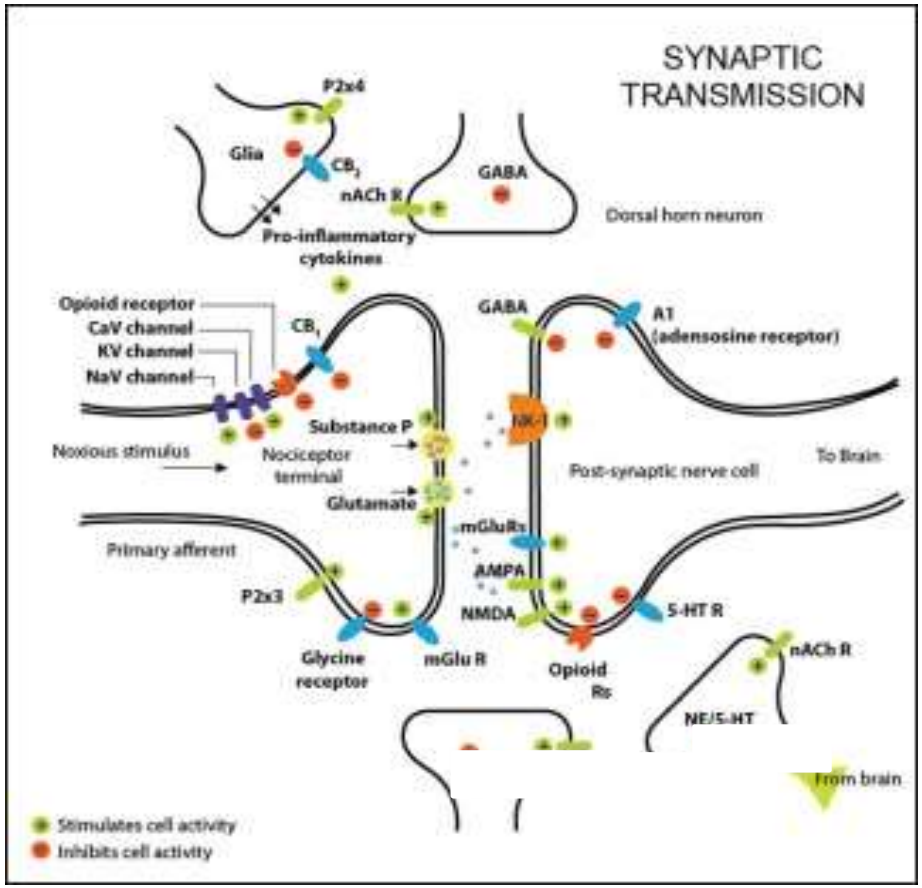
Hemispheric differences of gene expression, area 22

GO Set Name	Pletikos et al P Value	Hawrylycz et al P Value	Joint P Value	FDR
SYNAPTIC_TRANSMISSION	4.59E-06	4.5E-08	6.24E-12	6.25E-09
SIGNAL_TRANSDUCTION	2.99E-06	7.24E-07	6.04E-11	3.02E-08
GLUTAMATE_RECEPTOR_ACTIVITY	3.64E-09	0.004365	4.11E-10	1.33E-07
NERVOUS_SYSTEM_DEVELOPMENT	2.87E-07	8.02E-05	5.87E-10	1.33E-07
SYSTEM_DEVELOPMENT	2.03E-08	0.001291	6.64E-10	1.33E-07
TRANSMISSION_OF_NERVE_IMPULSE	1.30E-04	7.63E-07	2.38E-09	3.97E-07
MULTICELLULAR_ORGANISMAL_DEVELOPMENT	1.34E-07	0.001193	3.77E-09	5.39E-07
CELL_SURFACE_RECEPTOR_LINKED_SIGNAL_TRANSDUCTION_GO_0007166	1.53E-04	3.97E-06	1.35E-08	1.69E-06
RECEPTOR_ACTIVITY	4.40E-06	0.000171	1.66E-08	1.85E-06
CALCIUM_ION_BINDING	9.70E-06	0.000175	3.59E-08	3.59E-06
G_PROTEIN_COUPLED_RECEPTOR_PROTEIN_SIGNALING_PATHWAY	1.74E-04	1.09E-05	4.00E-08	3.64E-06
ANATOMICAL_STRUCTURE_DEVELOPMENT	4.88E-07	0.006619	6.64E-08	5.54E-06

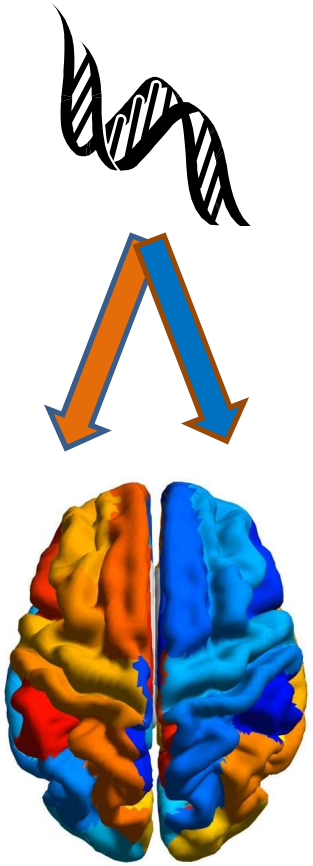
Karlebach & Francks, Cortex 2015

Hemispheric differences at the molecular level

- Left-right asymmetries of gene expression levels in adult auditory cortex
  - Synaptic transmission, glutamate receptor activity
  - Fine tuning of neuronal electrophysiology and neurotransmission



Genes involved in brain asymmetry



- Creation of L-R axis
  - Population-level asymmetry
  - Early embryonic origin, molecular chirality
- Degree of asymmetry
  - Downstream developmental cascades of many involved genes
  - Hemispheric regional specialization, white matter tracts
- Genes that support adult asymmetrical neurophysiology
  - Synaptic genes, ion channels

Genetics of brain asymmetry: consistent with aphasia research?

Wilson & Schneck 2020: Meta-analysis of fMRI studies of reorganization of language in post-stroke aphasia:

- Left hemisphere language regions are less activated in individuals with aphasia than in neurologically normal controls

- No compelling evidence for differential recruitment of additional left hemisphere regions or domain-general networks
- No compelling longitudinal evidence for dynamic reorganization of the language network.

- Modest, equivocal evidence that individuals with aphasia differentially recruit right hemisphere homotopic regions
- Modest evidence that left hemisphere language regions return to function over time

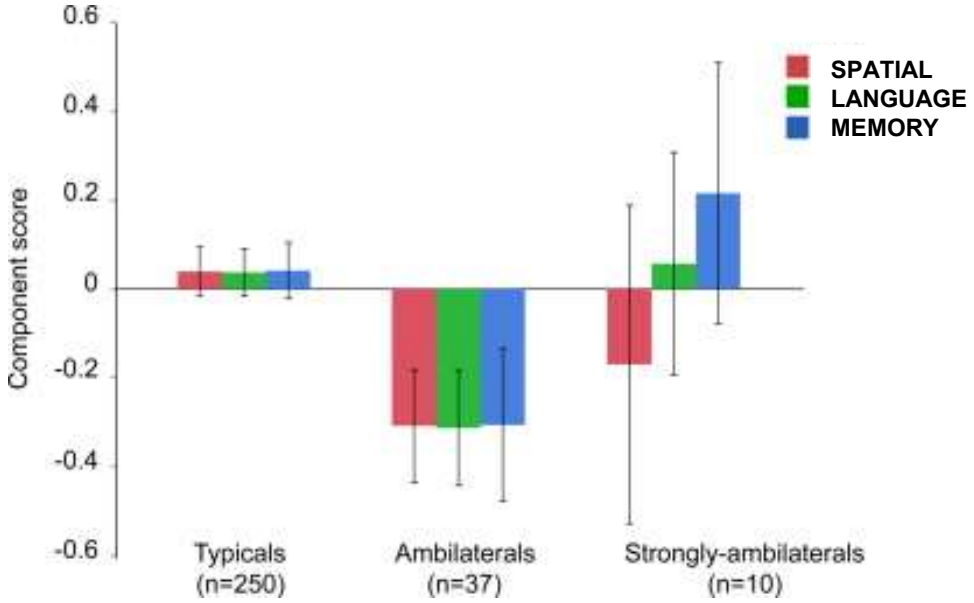
Genetic data suggest:

Population-level brain asymmetry arises through a genetically regulated program of development that is inherently asymmetrical from the start

Embryonic/fetal establishment of long-range network architecture is likely to limit scope for large-scale re-organizaton later in life

Synaptic gene expression is continuous throughout life, can be modulated to alter local neurophysiology and connectivity

Cognitive performance and language laterality



- Mild deficit associated with weaker functional lateralization for language production (Mellet *et al.* 2014)
- Cause, correlate, consequence? (Bishop 2013)