Multi-level integrated analysis of brain lateralization for language

Clyde Francks
Professor of Brain Imaging Genomics
Max Planck Institute – Radboud University Medical Center – Donders Institute
Nijmegen, the Netherlands

Multi-lateral

- HBP partnering project 2016-2019
- Mapping brain laterality (left-right asymmetry) at multiple levels: genetic effects, brain structure, brain function, cognitive variation and disorders

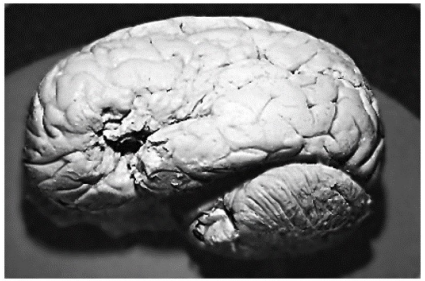
- Applicants & funding:

Clyde Francks (coordinating), Simon Fisher, Peter Hagoort
Max Planck Institute & Donders Institute, Nijmegen, The Netherlands

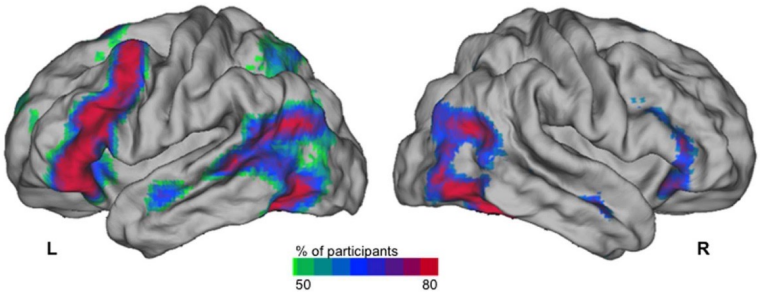
Fabrice Crivello, Bernard Mazoyer, Nathalie Tzourio-Mazoyer, Marc Joliot
Groupe d'Imagerie Neurofonctionelle, CNRS - CEA, Bordeaux University

Manuel Carreiras, Eugenio Iglesias, Alejandro Pérez, Cesar Caballero
Basque Center on Cognition, Brain and Language, Donostia-San Sebastian

Human brain laterality



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

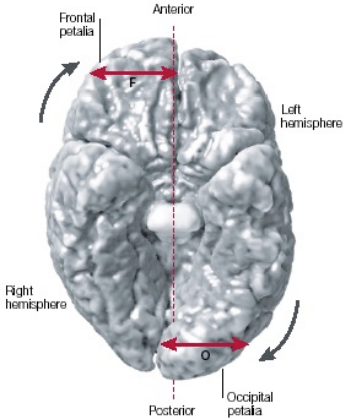


Covert sentence generation versus word list recitation (144 right-handers)

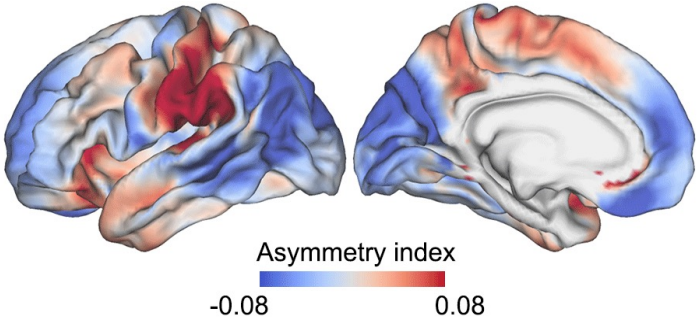
Mazoyer *et al*. 2014:

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

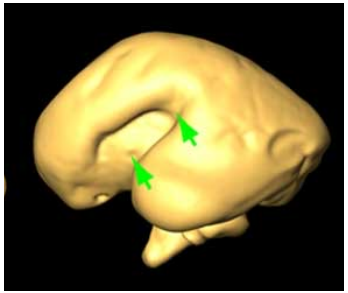
Hemispheric differences in brain structure



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



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



Middle gestation and onwards:
Structural lateralization of cerebral cortex (temporal lobe, perisylvian regions) Hering-Hanit et al. 2001

Altered structural brain asymmetry in autism spectrum disorder in a study of 54 datasets

Merel C. Postema, Daan van Rooij, [...] Clyde Francks

Nature Communications **10**, Article number: 4958 (2019)

Patterns of brain asymmetry associated with polygenic risks for autism and schizophrenia implicate language and executive functions but not brain masculinization

Zhiqiang Sha, Dick Schijven & Clyde Francks

Molecular Psychiatry (2021)

Atypical Brain Asymmetry in Autism—A Candidate for Clinically Meaningful Stratification

Dorothea L. Floris, Thomas Wolfers, Mariam Zabihi, Nathalie E. Holz, Marcel P. Zwiers, Tony Charman, Julian Tillmann, Christine Ecker, Flavio Dell'Acqua, Tobias Banaschewski, Carolin Moessnang, Simon Baron-Cohen, Rosemary Holt, Sarah Durston, Eva Loth, Declan G.M. Murphy, Andre Marquand, Jan K. Buitelaar, Christian F. Beckmann, and the EU-AIMS Longitudinal European Autism Project Group

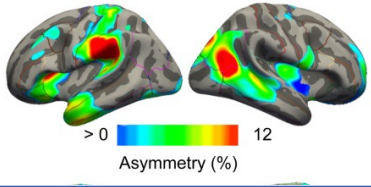
Biological Psychiatry:: 2021; 6:802–812

Elevated Levels of Atypical Handedness in Autism: Meta-Analyses

Paraskevi Markou, Banu Ahtam & Marietta Papadatou-Pastou

Neuropsychology Review **27**, 258–283 (2017)

Research themes



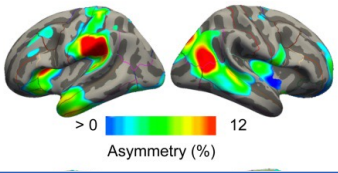
Theme 1:
- Mapping brain asymmetrical organization
- Structure, function, plasticity
- Behavioural correlates

- Pipelines for automated measurement of brain asymmetry in large datasets

- Biological insights, e.g. developmental basis
- Shared genetic effects on brain asymmetries and brain disorders

Theme 2:
- Genetic architecture of brain asymmetries

Publications from theme 1



Theme 1:

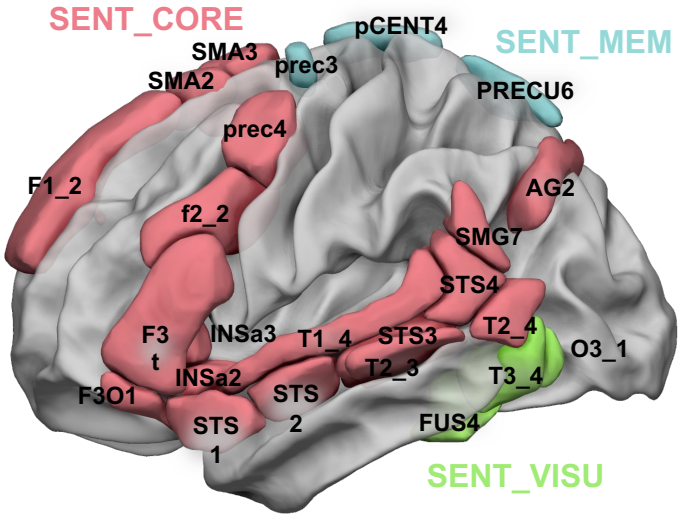
- Mapping brain asymmetrical organization
- Structure, function, plasticity
- Behavioural correlates

- Gurunandan et al. Verbal production dynamics and plasticity: functional contributions of language and executive control systems. Cereb Cortex. 2022
- Gurunandan et al. Converging Evidence for Differential Specialization and Plasticity of Language Systems. J Neurosci. 2020
- Branzi et al. Functional connectivity reveals dissociable ventrolateral prefrontal mechanisms for the control of multilingual word retrieval. Hum Brain Mapp. 2020
- Gurunandan et al. Functional plasticity associated with language learning in adults. Neuroimage 2019
- Hesling et al. Large-scale plurimodal networks common to listening to, producing and reading word lists: an fMRI study combining task-induced activation and intrinsic connectivity in 144 right-handers. Brain Struct Funct 2019
- Tzourio-Mazoyer et al. Intracortical Myelination of Heschl's Gyrus and the Planum Temporale Varies With Heschl's Duplication Pattern and Rhyming Performance: An Investigation of 440 Healthy Volunteers, Cerebral Cortex, 2018
- Labache et al. A SENtence Supramodal Areas AtlaS (SENSAAS) based on multiple task-induced activation mapping and graph analysis of intrinsic connectivity in 144 healthy right-handers. Brain Struct Funct, 2018
- Tzourio-Mazoyer et al. Is the planum temporale surface area a marker of hemispheric or regional language lateralization? Brain Struct Funct, 2017

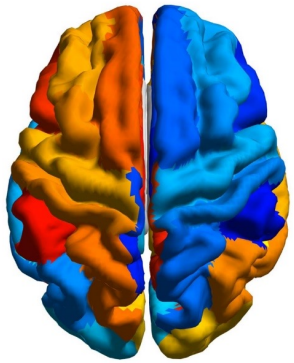
Theme 1 example output

- What are the essential language areas of the brain?

- Labache *et al*, Brain Structure & Function (2019)
- An atlas of high-order (sentence-level) language areas
  - Leftward asymmetrical activation during sentence-level tasks vs word lists
  - Conjunction across sentence production, reading, listening (supramodal)
  - 144 right-handed individuals
- Resting state-fMRI then used to define sub-networks



Research theme 2: 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?
  - Clues to pathways and mechanisms
  - Genetic overlaps with psychiatric traits can suggest shared mechanisms

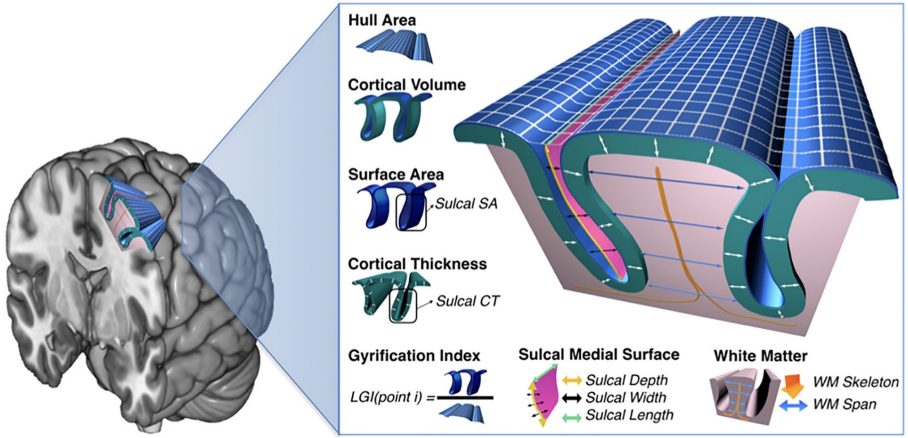
Publications from theme 2

- Sha et al. The genetic architecture of structural left–right asymmetry of the human brain. Nat Hum Behav 2021
- Sha et al. Handedness and its genetic influences are associated with structural asymmetries of the cerebral cortex in 31,864 individuals. PNAS 2021
- Kong et al. Large-scale phenomic and genomic analysis of brain asymmetrical skew. Cerebral Cortex 2021
- Carrion-Castillo et al. Genetic effects on planum temporale asymmetry and their limited relevance to neurodevelopmental disorders, intelligence or educational attainment. Cortex 2020
- Postema et al. The genetics of situs inversus without primary ciliary dyskinesia. Sci Rep 2020
- De Kovel et al. A large-scale population study of early life factors influencing left-handedness. Sci Rep, 2019
- Carrion-Castillo et al. Genome sequencing for rightward hemispheric language dominance. Genes Brain Behav. 2019
- Francks, C. In search of the biological roots of typical and atypical human brain asymmetry. Phys Life Rev. 2019

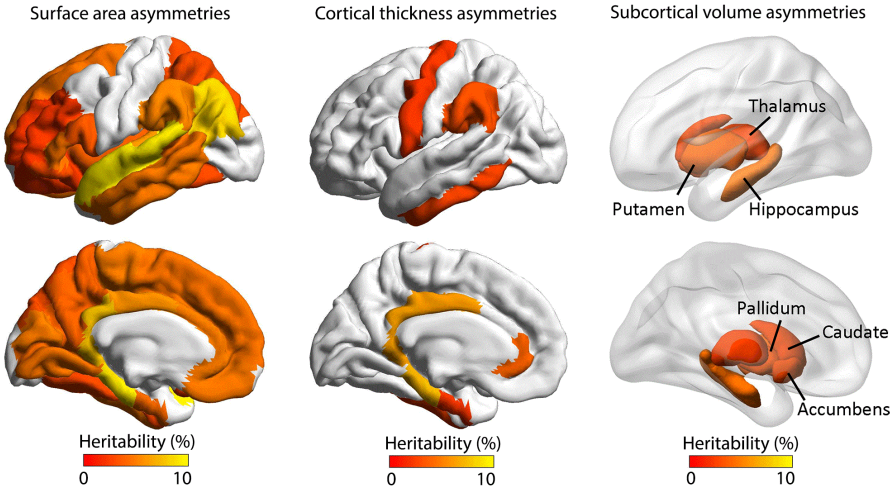
Theme 2:

- Genetic architecture of brain asymmetries

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



Carmona et al., 2019



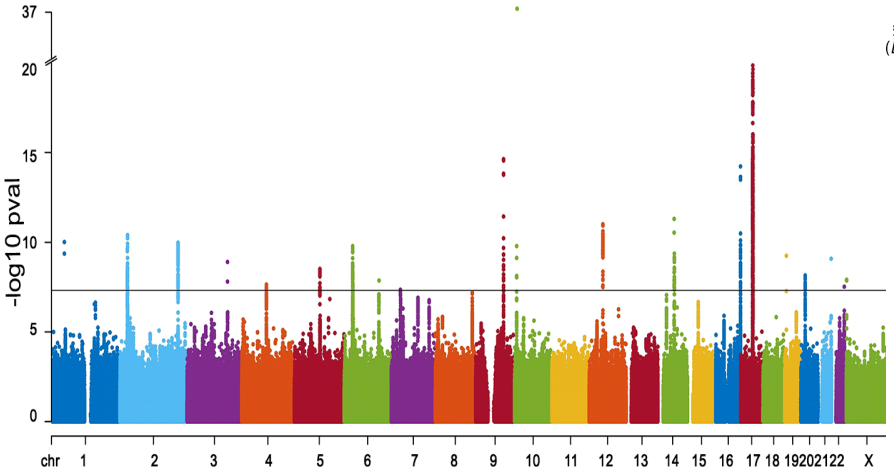
- Freesurfer automated cortical parcellation and subcortical volume measurement
- Left and right homologous regional measures
- Asymmetry index for each individual and region (L-R)/((L+R)/2)

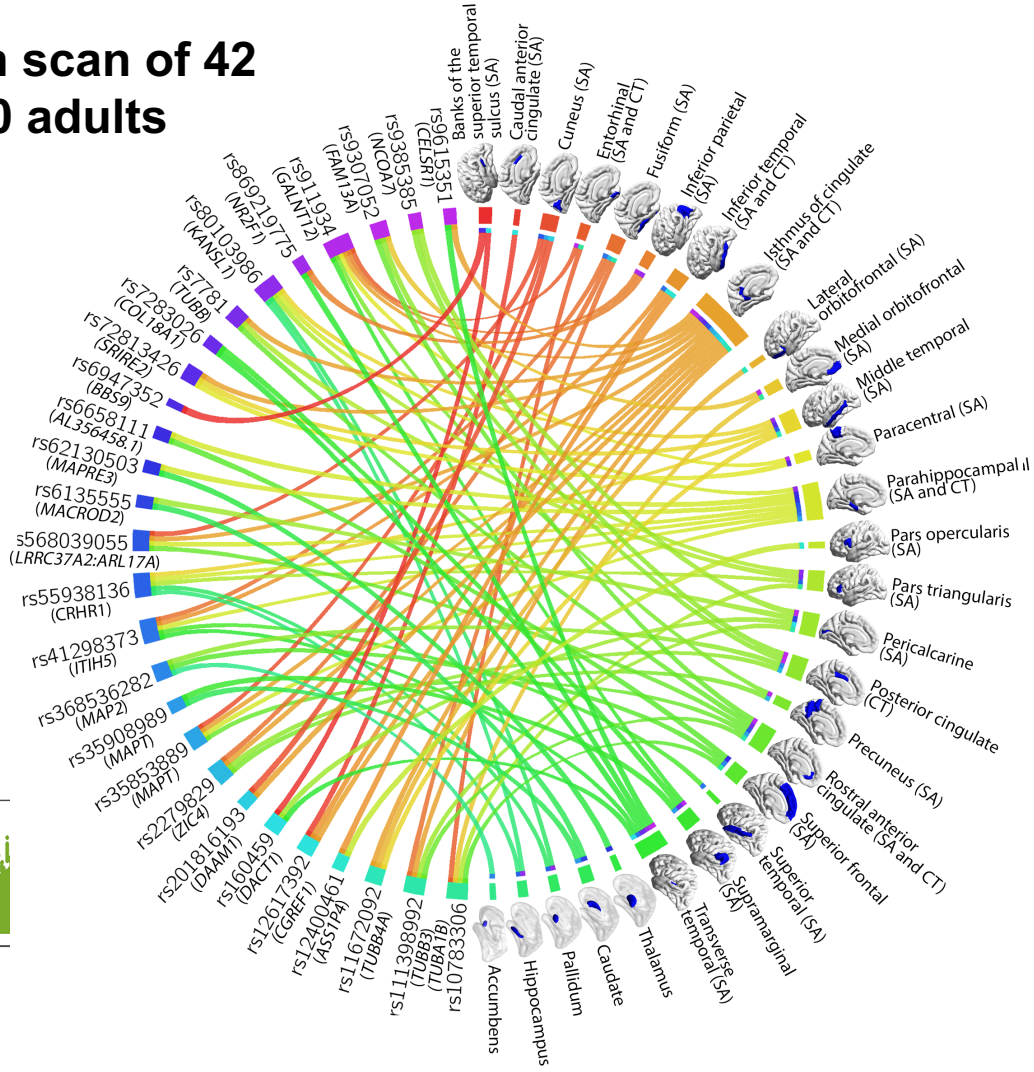
- Forty-two regional asymmetries showed significant SNP-based heritabilities (p_{FDR}<0.05), from 2.2% to 9.4%

Sha et al. Nat Hum Behav 2021

Multivariate genome-wide association scan of 42 regional brain asymmetries in >32,000 adults

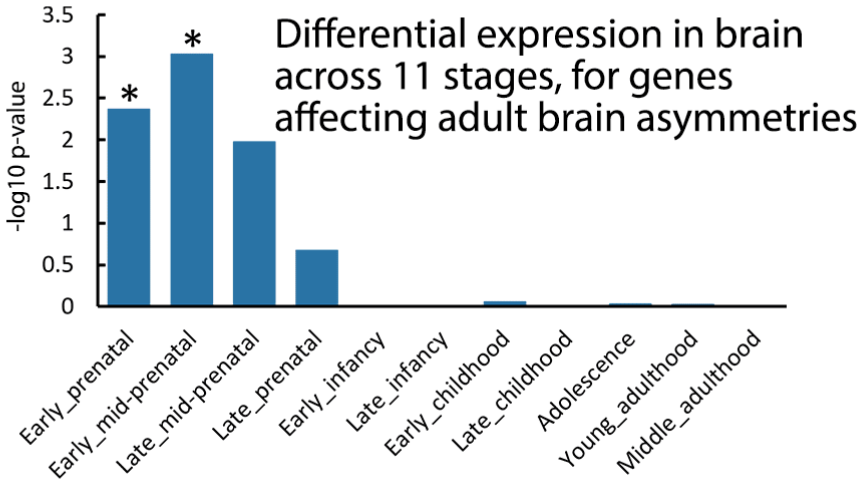
- 21 genomic loci associated with variation in adult brain structural asymmetry

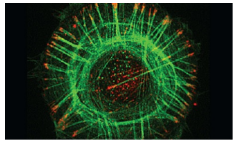




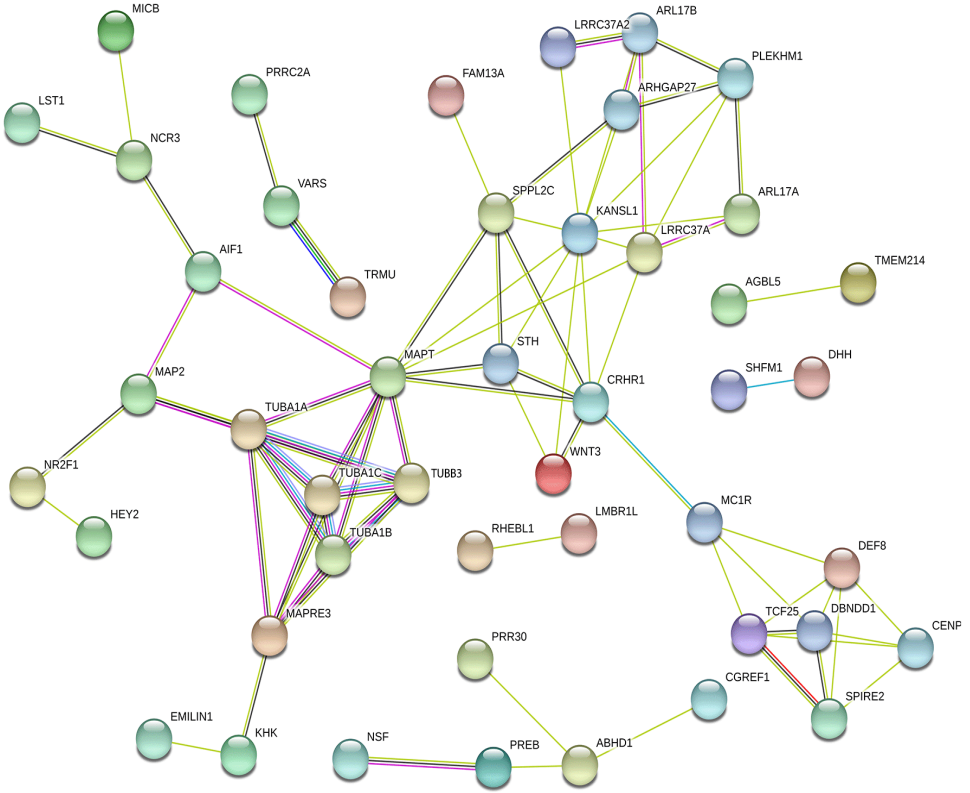
Sha et al. Nat Hum Behav 2021

Genes associated with variation in adult brain asymmetry



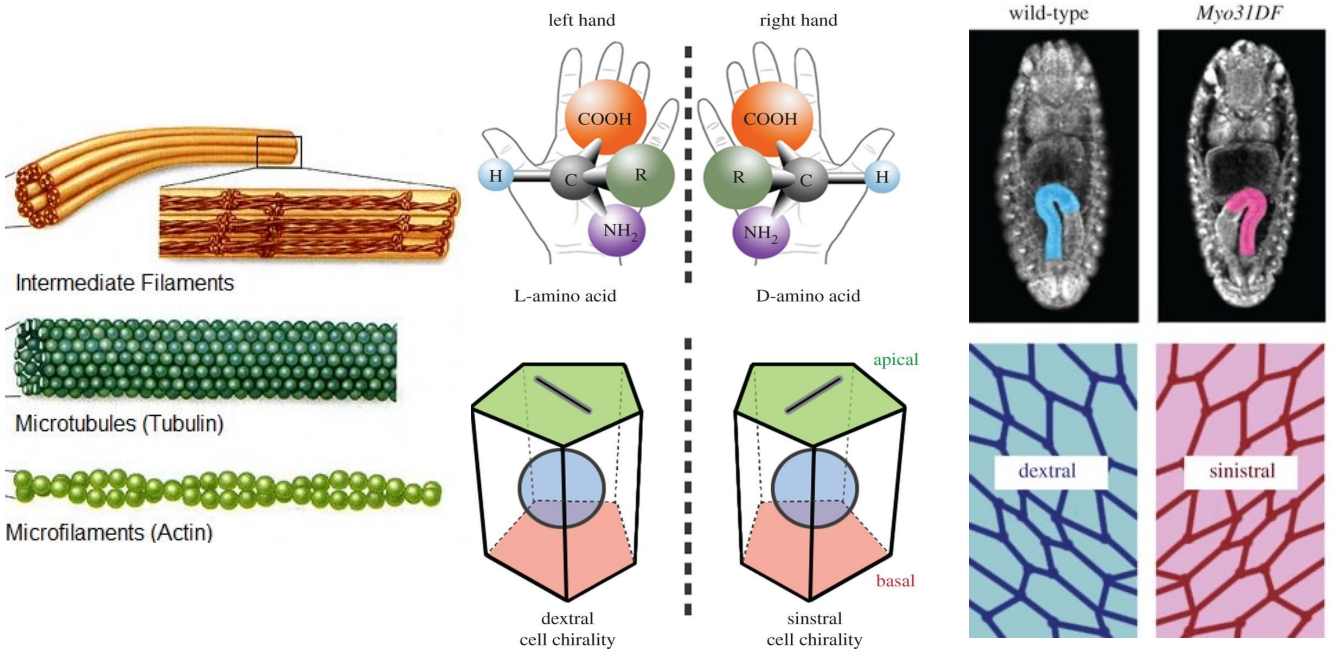


- Enrichment for microtubule-related functions
- Likely to affect the cytoskeleton (internal protein skeleton of cells) – controls cell shape, movement, internal transport, growth



Sha et al. Nat Hum Behav 2021

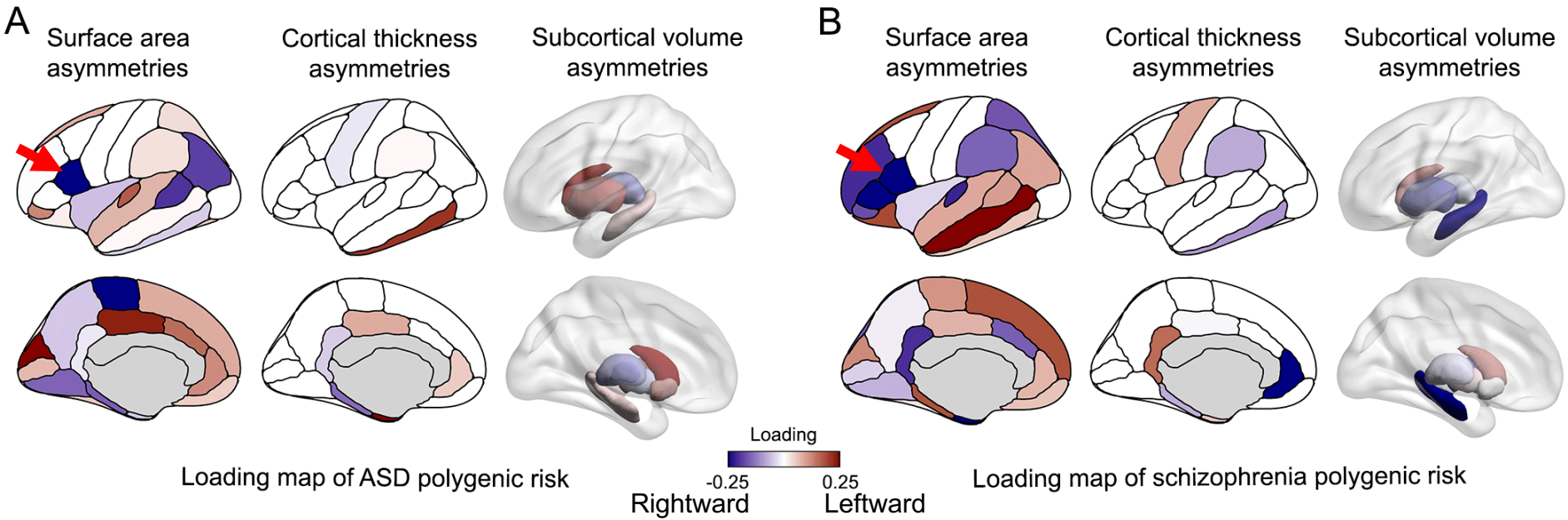
Cellular chirality for L-R axis formation of the brain?



- 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

Multivariate associations of disorder polygenic risks with 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 a more male-like or female-like average brain asymmetry pattern (no evidence for extreme male brain with increased autism polygenic risk)

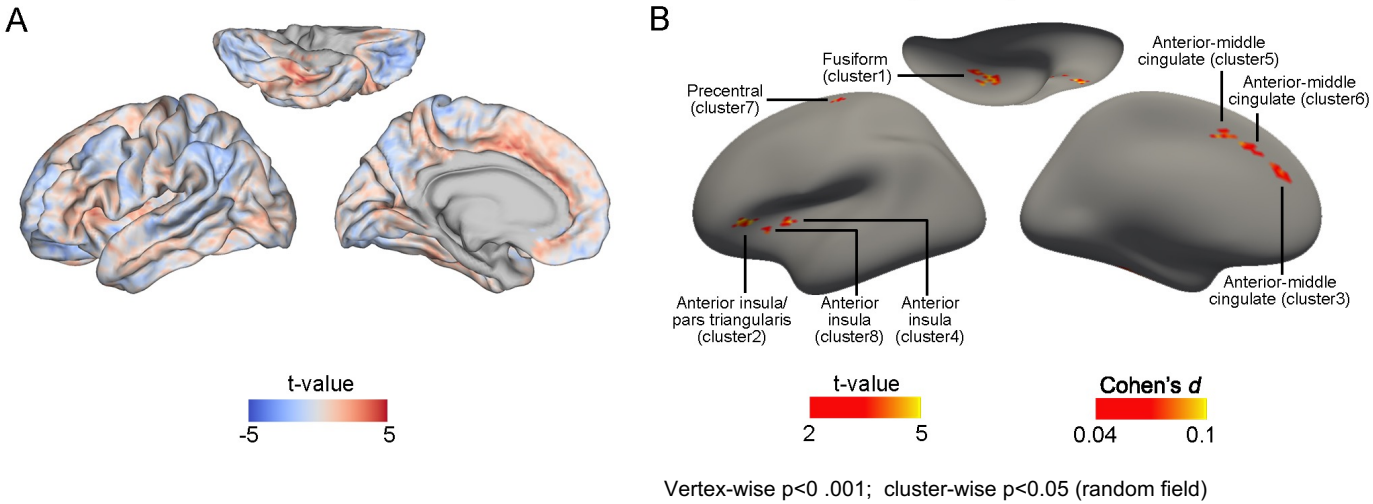
Handedness & cortical asymmetry

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

- All ten clusters showed rightward shift of asymmetry in left-handers
- Increased neural resources in right hemisphere for left hand control

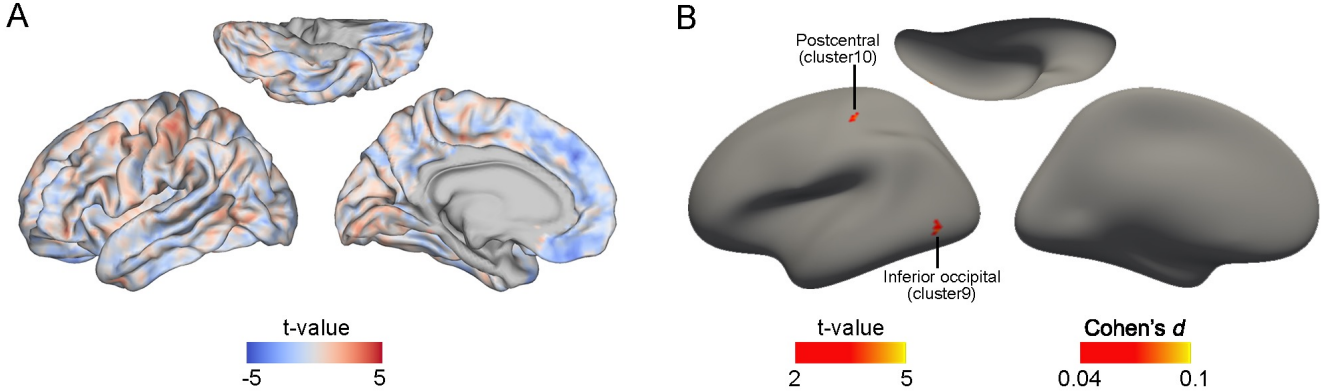
Sha et al. PNAS 2021

Handedness-associated surface area asymmetry



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

Handedness-associated cortical thickness asymmetry

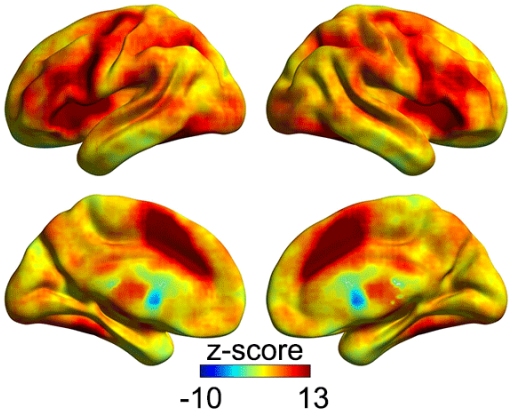


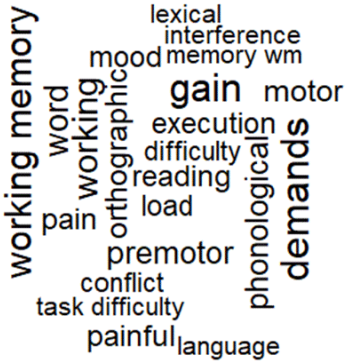
Functional annotation of handedness-associated cortical regions

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

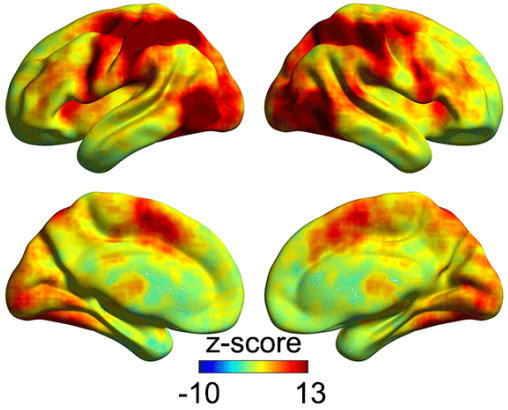
A

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



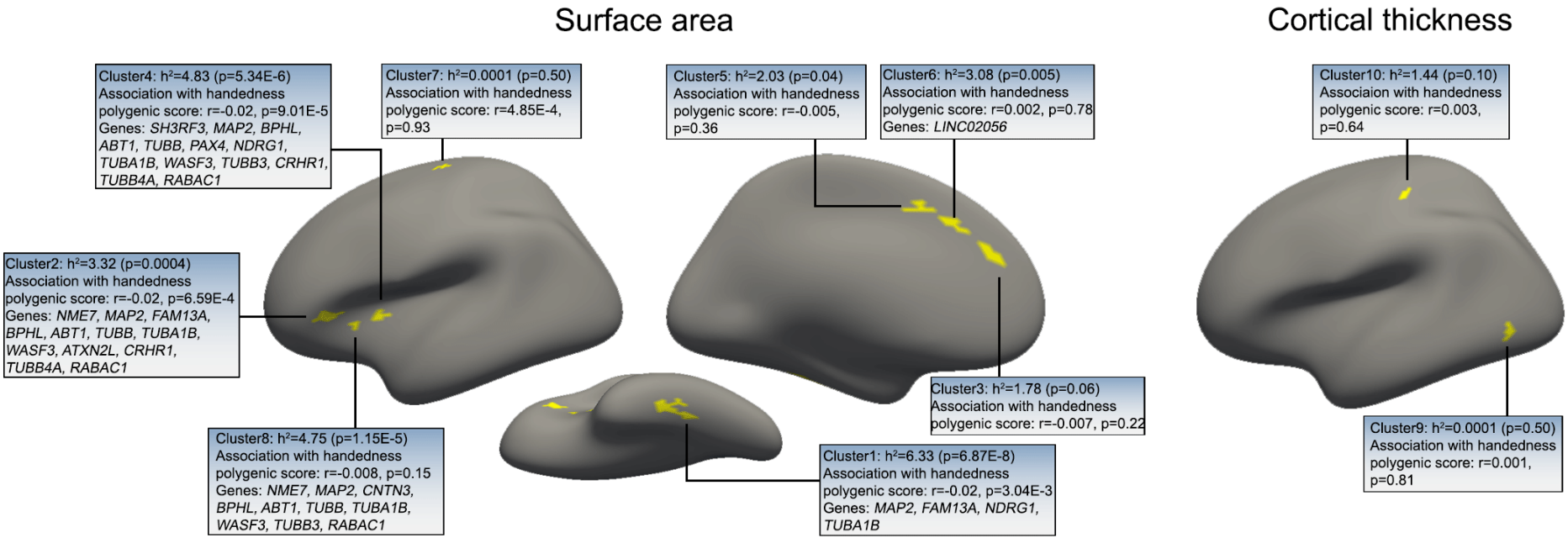


fMRI-based functional annotation of regions showing associations of their cortical thickness asymmetries with hand preference



Sha et al. PNAS 2021

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

ENIGMA-Laterality working group

Large-scale studies of human brain asymmetry in health & disease (no genetics so far)

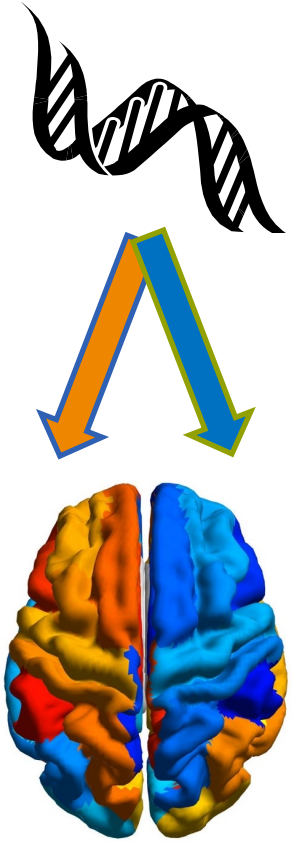
- Guadalupe et al. Human subcortical brain asymmetries in 15,847 people worldwide reveal effects of age and sex. ***Brain Imaging and Behavior*** (2017).
- Kong et al. Mapping cortical brain asymmetry in 17,141 healthy individuals worldwide via the ENIGMA Consortium. ***PNAS*** (2018)
- Postema, et al. Altered structural brain asymmetry in autism spectrum disorder in a study of 54 datasets. ***Nature Communications*** (2019)
- de Kovel et al. No alterations of brain structural asymmetry in major depressive disorder: an ENIGMA consortium analysis. ***Am J Psychiat*** (2019)
- Kong et al. Mapping cortical and subcortical asymmetry in obsessive-compulsive disorder: Findings from the ENIGMA Consortium. ***Biological Psychiatry*** (2020)
- Kong et al. Reproducibility in the absence of selective reporting: An illustration from large-scale brain asymmetry research. ***Human Brain Mapping*** (2020).
- Kong et al. Mapping brain asymmetry in health and disease through the ENIGMA consortium. ***Human Brain Mapping*** (2020).
- Postema et al. Analysis of structural brain asymmetries in Attention-Deficit/Hyperactivity Disorder in 39 datasets. ***Journal of Child Psychology and Psychiatry*** (2021)
- Sha et al. Subtly altered topological asymmetry of brain structural covariance networks in autism spectrum disorder across 43 datasets.. ***Molecular Psychiatry*** (2021)
- Schijven et al. Large-scale analysis of structural brain asymmetries in schizophrenia via the ENIGMA consortium. **medRxiv.org** (2022)

On-going/planned studies:

- Brain asymmetry in typical childhood development
- Brain asymmetry in epilepsies
- Brain asymmetry in bipolar disorder
- Contact: clyde.francks@mpi.nl; e.lueders@auckland.ac.nz

Conclusions – genetics of brain asymmetry

- Large-scale studies have started to answer long-standing questions about human brain asymmetry
    - Which genes are associated with brain asymmetry
    - Which regional asymmetries are associated with handedness or psychiatric traits, and how strongly
    - Gene-brain-handedness associations
- Genes affecting adult brain asymmetry are especially active during embryonic brain development (but not only)
- Microtubule involvement hints at a cellular chirality mechanism of brain L-R axis formation
    - Possibly very early initiation in embryonic development



Practical issues & next steps

- Since conceiving the project in 2014...
  - UK Biobank – large sample for genetic discovery but no language task fMRI
    - Re-directed efforts to genetics of structural asymmetry
    - Currently working on genetics of resting-state connectivity asymmetry, and rare genetic mutations (exome sequences)

- Large-scale genetic studies of reading/language performance only just published in 2022 (GenLang, 23andMe)
  - Genetic overlaps between brain asymmetries and reading/language performance

- New research line: The mouse as a model for brain asymmetry and its genetic contributions
  - Knockout lines for genes implicated by human work
  - Spatial transcriptomics, immunohistochemistry, histology, MRI

- EBRAINS: No usage so far (e.g. UK Biobank data cannot be deposited there)
  - Suitable for future mouse data?

biobank uk
Enabling scientific discoveries that improve human health

medRxiv
Discovery of 42 Genome-Wide Significant Loci Associated with Dyslexia
Catherine Doust, Pierre Fontanillas, Else Eising, Scott D Gordon,

PNAS RESEARCH ARTICLE | PSYCHOLOGICAL AND COGNITIVE SCIENCES GENETICS

Genome-wide analyses of individual differences in quantitatively assessed reading- and language-related skills in up to 34,000 people

Thanks!

Amaia Carrion Castillo, Carolien de Kovel, Merel Postema, Xiangzhen Kong, Zhiqiang Sha, Simon Fisher, Peter Hagoort, Clyde Francks (coordinating)
Max Planck Institute & Donders Institute, Nijmegen, The Netherlands

Anonietta Pepe, Loïc Labache, Isabelle Hesling, Fabrice Crivello, Bernard Mazoyer, Nathalie Tzourio-Mazoyer, Marc Joliot,
Groupe d'Imagerie Neurofonctionelle, CNRS - CEA, Bordeaux University

Kshipra Gurunandan, Francesca Branzi, Cesar Caballero, Alejandro Pérez, Amaia Carrion Castillo, Manuel Carreiras
Basque Center on Cognition, Brain and Language, Donostia-San Sebastian