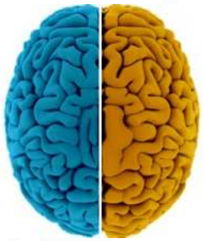
MULTI-LATERAL



Multi-Level Integrated Analysis of Brain Lateralization for Language

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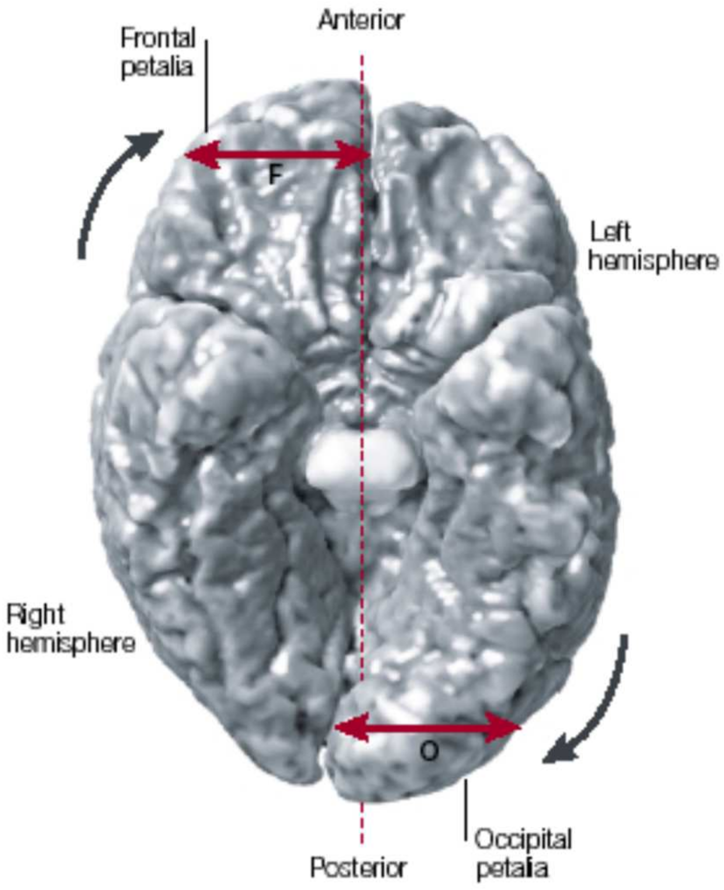
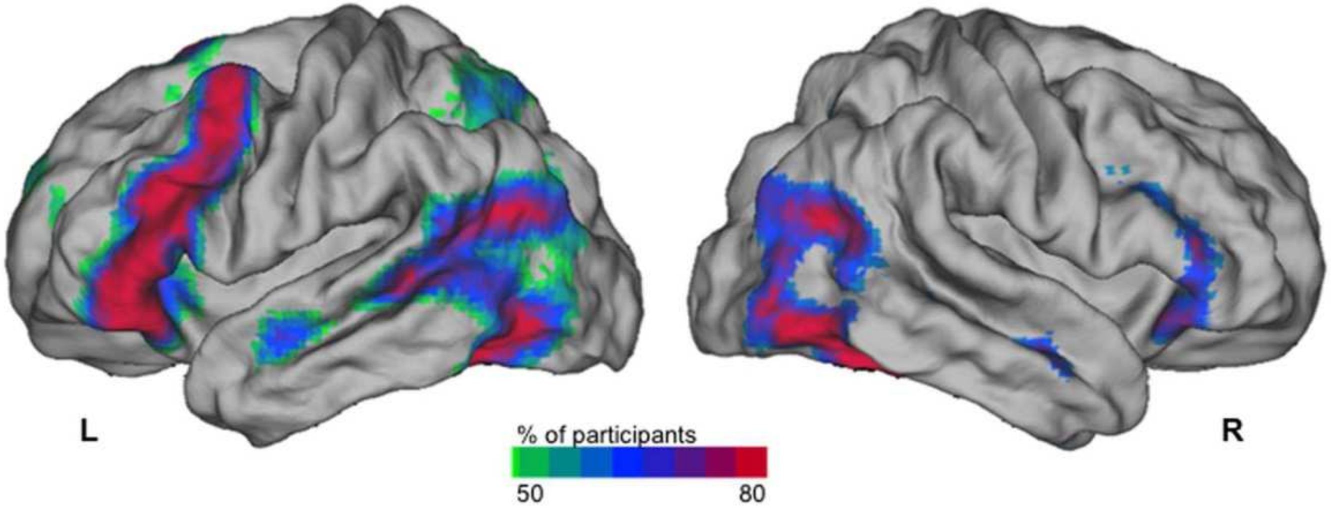
Left-right lateralization



Toga & Thompson 2003

- Many functions and behaviours lateralized to a degree
  - Language, visuospatial cognition, hand motor control
  - Behavioural and anatomical lateralization *in utero*
    - *Perisylvian language regions*
- Genetic basis largely unknown

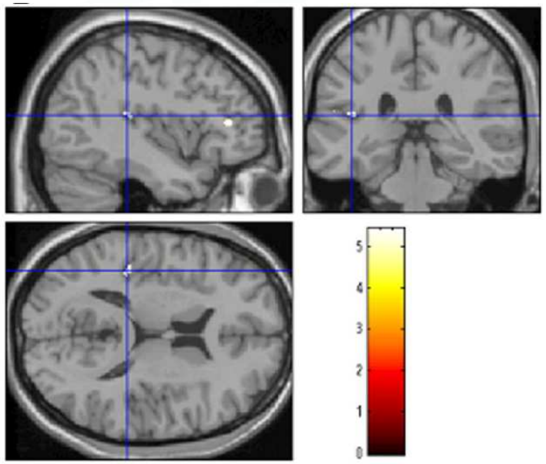
Language production



- Probability map of having a significant activation during sentence generation as compared to word list recitation in 144 right-handers
  - Areas involved in lexico-semantic and syntactic processing
  - Mazoyer et al. 2014

Lateralization and disorders

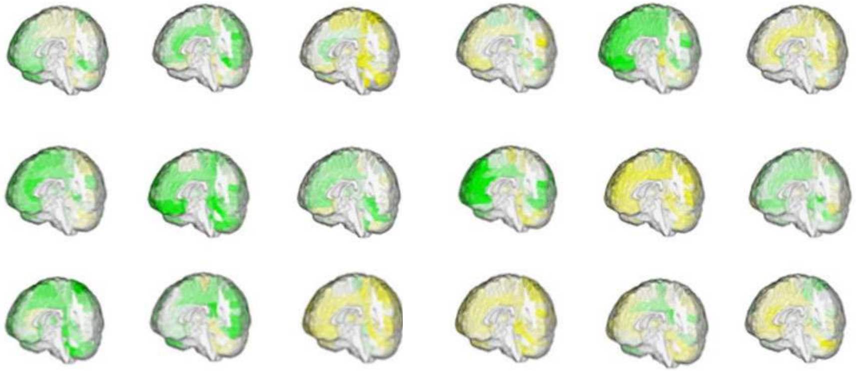
- Alterations of typical lateralization
  - Structural and functional imaging
  - Schizophrenia, language impairment, dyslexia, autism
  - Reductions or reversals of normal lateralizations
  - Not in all study populations
  - Verbal and spatial ability (non-disorder)
  - Causal relations unclear



Kawasaki *et al*. Biol Psych 2008

Reviewed by Renteria, M. in Twin Research and Human Genetics 2012

Human brain diversity

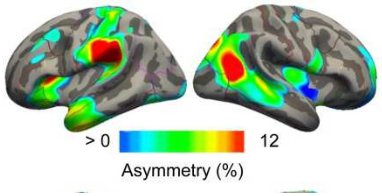


Berman & Joel 2015

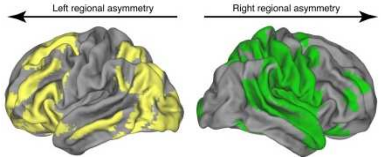
- The ‘typical brain' is the focus of much HBP activity, but brain diversity is also important
- Language lateralization as a test case:
  - Pinpointing shared genetic effects on variation in lateralization and cognition would discriminate causal relations
- Genetic analysis of human quantitative traits requires data from thousands of study participants
  - Individual genetic effects are small
  - Automated image analysis methods are essential
- Perisylvian language-related cortex is highly variable anatomically
  - Current automated methods do not perform optimally

Outline of the project

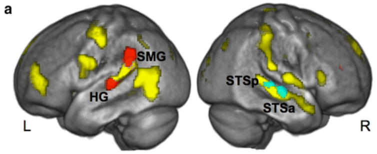
WP1. Improved automated measures of brain structural lateralization, global and regional (torque, grey matter hemispheric asymmetries, temporal, Heschl's gyrus)



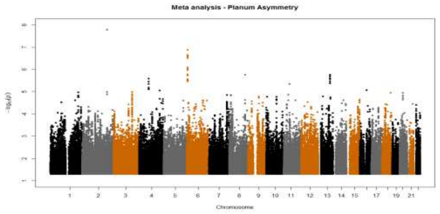
WP2. Improved automated measurement of intrinsic connectivity lateralization to predict language task-related functional activation



WP3. Measurement of language-task related functional lateralization (spatial and temporal, concurrent fMRI/EEG in a new dataset) and structure-function relationships



WP4. Application of above methods to multiple large datasets for genome-wide association meta-analysis, heritability/polygenics, integrate post mortem mRNA data



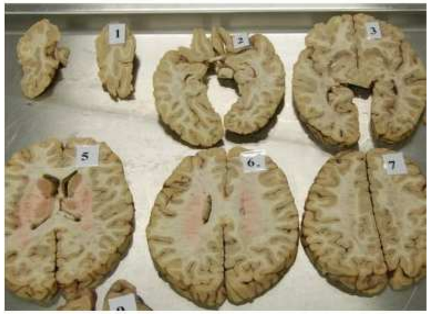
WP5. Test sets of genes that are linked to language lateralization, in relation to variation in language- and reading-related performance

Transcriptome analysis in the adult superior temporal cortex

- Contrast mRNA levels, left and right homologous regions (BA22)
- Fine tuning neuronal electrophysiology and neurotransmission

Gene Ontology Set	FDR
SYNAPTIC_TRANSMISSION	6.25E-09
SIGNAL_TRANSDUCTION	3.02E-08
GLUTAMATE_RECEPTOR_ACTIVITY	1.33E-07
NERVOUS_SYSTEM_DEVELOPMENT	1.33E-07
SYSTEM_DEVELOPMENT	1.33E-07
TRANSMISSION_OF_NERVE_IMPULSE	3.97E-07
MULTICELLULAR_ORGANISMAL_DEVELOPMENT	5.39E-07
CELL_SURFACE_RECEPTOR_LINKED_SIGNAL_TRANSDUCTION	1.69E-06
RECEPTOR_ACTIVITY	1.85E-06
CALCIUM_ION_BINDING	3.59E-06
G_PROTEIN_COUPLED_RECEPTOR_PROTEIN_SIGNALING	3.64E-06
ANATOMICAL_STRUCTURE_DEVELOPMENT	5.54E-06

Karlebach & Francks, Cortex 2015



Outcomes

- HBP project linking from genetics through neuroimaging to cognitive performance
- Improved automated methods for analysis of large numbers of brain images
- Possible definition of susceptibility factors for important subtypes of impaired cognition
- Genes and the brain’s ‘third axis’: Fundamental question in human neuroscience
- Compare genetic data with HBP receptor mapping data
- Future cellular, computational, animal models
  - Manipulate lateralized gene sets
  - Neuronal signalling, computation
  - Left-right contrast: how neural networks are fine-tuned to support functions such as language