MULTI-LATERAL: Multi-level Integrative Analysis of Brain Lateralization for Language

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Abstract

Left-right lateralization is an important organizing principle of the human brain which is not a current focus of HBP research. One prominently lateralized anatomical and functional network underlies the uniquely human ability to speak and understand language. A lack of brain lateralization has been associated with variation in human cognitive abilities important to language, and also with susceptibility to neurocognitive disorders including language impairment, dyslexia, autism and schizophrenia. The genetic basis of human brain lateralization is unknown, while links between lateralized anatomy and function are poorly understood. It is likely that genes involved in lateralization, both developmentally and during adult function, contain variants in the population that influence cognitive performance and neurocognitive disorders. We are generating transcriptomic data on lateralized gene expression in the embryonic and adult human brain. We recently identified, for the first time, sets of neuronal genes in the healthy adult brain that are expressed at different levels in the left and right temporal cerebral cortex (crucial for the language network). Here we propose a multi-level and integrated analysis of brain lateralization for language: I. Develop improved methods to reliably and automatically measure individual differences in lateralization of the language network in large numbers of participants, for anatomy, resting state intrinsic connectivity, and task-related function. The language cortex is a variable region for which current automated methods do not perform optimally, yet automated methods are essential for achieving large datasets that are statistically powered for genetic studies. It is essential to understand human brain diversity, as well as researching the 'average brain' which is the focus of most HBP activity. II. Apply the methods in brain imaging datasets having genetic data available, for the purposes of association and rare variant analysis followed by integrated genome-level analysis with transcriptomic (lateralized gene expression) data and genomic gene-set analysis. These combinatorial analyses go beyond standard genome-wide association scanning. Rather, the genomic data will be utilized to merge multiple genetic signals, informed by gene expression data and gene function data, in order to increase statistical power. III. Relate the gene sets arising from step II to human cognitive variability linked to reading and language, and susceptibility to neurocognitive disorders. Again, evidence-based combinations of genetic variants, constructed over many genes, will be investigated. Pinpointing shared genetic effects on lateralization and cognition would discriminate causal relations from mere correlation. Outcomes from this research program will include improved technology for automated analysis of large numbers of brain scans, and possible definition of susceptibility factors for important subtypes of impaired cognition.

Consortium

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