Population & imaging genetics approaches: what can brain imaging contribute?

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Symposium
Monday - Symposia AM

The integration of imaging and genetic/epigenetic data in population neuroscience studies enables elucidation of the links between brain regions/networks, genes, and gene-environment relationships, and importantly the integration of biological pathways. Imaging genetics approaches have evolved from candidate gene studies where simple correlative analysis of one or a small number of genes is replaced with genome wide analysis (GWAS), which provide a more comprehensive view of the often complex underlying relationships. A variety of analysis approaches have been utilized including massive univariate correlation on one end to the use of multivariate data-driven approaches such as independent component analysis on the other end. In this symposium we discuss some of the major ongoing efforts in imaging genetics including large harmonized studies such as generation R and the UK biobank as well as meta-analytic approaches such as the international ENIGMA study. In addition, we highlight some of the interesting informatics tools and data sets that can be brought to bear on such studies including an analysis of cross-tissue effects (e.g. brain, blood, saliva) and their relationship to brain imaging data. Various important data processing steps will be highlighted including quality control, the impact of sex and ethnicity, batch effects, and more with the target audience being those who have imaging experience and are interesting in expanding to imaging genetics.

Objective

1) To provide a brief overview of imaging genetics concepts, survey some of the many different ways it can be used, and motivate its application to study the human brain.
2) To show several examples of large ongoing imaging (epi)genetic population neuroscience studies which have already yielded important new information about the link between brain imaging and genetics in health and disease.
3) To introduce the audience to the various analytic approaches including integration with bioinformatics tools, quality control issues related to imaging genetics, and advanced data fusion approaches.

Target Audience

Talks will be structured to be accessible to both beginners to brain imaging who have taken the preconference course, as well as to more advanced users who are interested in the use of imaging genetics approaches to study brain imaging data.

Co Organizer

Jingyu Liu, The Mind Research Network

Organizer

Vince Calhoun, Mind/UNM

Presentations

Cross-tissue investigation of the interplay of genetics, epigenetics and brain in schizophrenia (index.cfm?do=ev.viewEv&ev=1660)

Recent GWAS studies have presented a much more detailed picture of the genetic risks to schizophrenia, which will unequivocally guide future in-depth investigations on the etiology and pathophysiology of schizophrenia. We present an investigation of multi-level information from DNA coding, DNA methylation and gene expression, to brain structure

and function, aiming at filling the gap between the genetic risks to overt symptoms, and providing insight to the possible mechanisms that genetic risks exert the effect. Focusing on the schizophrenia risk regions highlighted by GWAS, we first studied methylation quantitative trait loci (meQTL) effects, where risk SNPs regulate cis DNA methylation level. These meQTL effects are validated across tissue types (post-mortem brain, blood and saliva). Extended to whole genome, we also characterized cross-tissue meQTLs and targeted methylation cites (CpGs) in terms of genomic and genic locations, involvement of diseases, particularly schizophrenia, enrichment of expression QTLs (SNPs that regulate gene expression), and cross-tissue methylation correspondence. These results support the role of DNA methylation in the etiology of schizophrenia, and also the usage of peripheral tissues in the study of schizophrenia. To further explore the peripheral DNA methylation relevance to brain, we tested the associations between DNA methylation of risk regions and brain structure. Our findings demonstrated that epigenetics carry stronger associations with brain structure than genetics. We identified one specific genetic association from chromosome 6 with brain structure, and the risk SNPs presented cross-tissue regulation effects on DNA methylation and gene expression. Together, our studies showed the importance of mining multi-level information in the study of schizophrenia.

Presenter

Jingyu Liu, The Mind Research Network

Brain developmental differences associated with polygenic and polyenvironmental risk for neurodevelopmental disorders in school age children (index.cfm?do=ev.viewEv&ev=1661)

The complexity and heterogeneity associated with major psychopathology, such as schizophrenia and mood disorders, are thought to be the result of multiple genes, each which contribute a small amount to the illness. Recently there has been an exponential increase in studies utilizing independent genome wide association study (GWAS) analyses (i.e., the Psychiatric Genomics Consortium) to create polygenic risk scores for multiple psychiatric disorders. These scores can provide a metric for genetic susceptibility for children to later develop a psychiatric disorder. Similar to polygenic risk scores, large epidemiological studies have the ability to also assess the role of environmental factors associated with brain development. Using a similar ‘polygenic hypothesis’ of emerging psychopathology, it’s also possible that multiple environmental factors combine such that there is a ‘polyenvironmental’ risk for psychopathology. The goal of this presentation is to discuss specific brain findings associated with both genetic and environmental risk in school age children. We will also discuss novel uses of polygenic scores to assess neuroscience questions in typically developing children. This work is nested within the Generation R Study, a large epidemiological study of child development.

Presenter

Tonya White, MD, PhD, Erasmus University Medical Centre

Imaging genetics from a worldwide perspective (index.cfm?do=ev.viewEv&ev=1662)

The ENIGMA project (Enhancing NeuroImaging Genetics through Meta Analysis, www.enigma.ini.usc.edu) is a collaborative network of researchers with neuroimaging and/or genome-wide scan data. It leverages the many imaging studies around the world, to identify the imaging measures that can be compared meaningfully across studies, and to obtain the best estimate of the effect size through meta-analysis. Similarly for imaging and genetics studies: Each sample is underpowered in its own right, but through careful prospective meta-analysis the consensus

effect sizes for genetic effects on imaging measures can be quantified. I will review the methods of the ENIGMA project and the example findings, from within-disorder analyses of brain structures to cross disorder comparisons (currently over 25 disease groups are participating), and imaging genetics incorporating data from a subset of over 30,000 subjects. The meta-analyses of these projects have led to a renewed interest in mega-analyses, requiring more intrusive data sharing; however, I will also present on methods for distributed data analysis for the benefits of mega-analysis without loss of confidentiality.

Presenter

Jessica Turner, Georgia State University

GWAS of brain structure and function from 15,000 UK Biobank participants (index.cfm?do=ev.viewEv&ev=1663)

Joint analysis of genetic and brain imaging UK Biobank datasets presents a unique opportunity for uncovering the genetic bases of brain structure and function, including genetic factors relating to brain development, ageing and disease. We carried out genome-wide association studies of 3,144 distinct brain imaging derived phenotypes (IDPs) from UK Biobank data. We will present hundreds of significant associations between genetic regions and IDPs, and analyses showing that half of the IDPs have significant heritability. Notable significant associations include: iron-related genes linked to T2* in subcortical regions; extracellular matrix associated with white matter microstructure and lesion volume; genes regulating midline axon guidance related to pontine crossing tract organisation. More broadly, effects were mainly seen in imaging measures associated with genes involved in brain development and transport of nutrients. Genes implicated in neurodegenerative disorders were largely related to iron and cardiovascular traits, and to brain development for psychiatric disorders. Over the next few years, the number of participants with imaging data will gradually increase to 100,000, which will allow a much more complete discovery of the genetic basis of human brain structure, function and connectivity. (We are grateful to UK Biobank for making the resource data available. Funding from the UK MRC, Wellcome Trust, ERC.).

Presenter

Fidel Alfaro Almagro, FMRIB Centre, WIN, University of Oxford