Brain connectivity is modularly represented in the genome

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Abstract

The network organization of human brain functional connectivity is strikingly similar to that of inter-regional gene coexpression. Yet, whether gene coexpression explains functional connectivity with an accuracy that is equivalent across the cortex, or whether different sets of genes explain distinct aspects of functional connectivity remains unknown. Furthermore, it is unclear how the relationship between gene coexpression and brain connectivity might change over development, relate to heritability, and track behavior. Here, we leverage several large multimodal data sets to demonstrate that different sets of genes statistically account for different aspects of brain network architecture. Critically, gene coexpression is more strongly related to functional connectivity than to structural connectivity. Brain regions whose connections are well fit by gene coexpression also tend to have connections whose strengths are commonly shared across humans, co-vary with behavior, and display stereotyped development over adolescence. In contrast, brain regions whose connections are not well fit by gene coexpression tend to connect diverse functional network modules and be strongly heritable. Our results lend support to the notion that functional connectivity is modularly represented in the genome and mediates between genotypes and cognitive phenotypes.

Keywords: network neuroscience; gene expression; development

Recent work has uncovered a statistical association between the strength of functional connectivity between two regions of the human brain and the similarity of gene transcription—gene coexpression—between those regions (Hawrylycz et al., 2012; 2015; Krienen, Yeo, Ge, Buckner, & Sherwood, 2016; Richiardi et al., 2015). Related cross-species work has shown that while gene expression variance accounts for most phenotypic variance between species, gene expression in the brain is generally conserved across species (Khaitovich, Enard, Lachmann, & Pääbo, 2006). However, closer inspection of specific neuroanatomical features has revealed that the transcriptional profiles of a subset of genes enriched in supragranular layers in the human (compared to the mouse) are more similar between regions with long range cortico-cortico connections, suggesting both regional and species specificity (Krienen et al., 2016). Critically, whether gene coexpression explains functional connectivity with an accuracy that is equivalent across the cortex and whether different sets of genes explain distinct aspects of functional connectivity remains unknown. Moreover, brain network organization as manifest in both structural (Jahanshad et al., 2012; Kochunov et al., 2015; Zhu et al., 2015) and functional connectivity (Glahn et al., 2010; Jansen, Mous, White, Posthuma, & Polderman, 2015; van den Heuvel et al., 2013) is heritable. Yet, exactly how that organization, its developmental trajectory, and its impact on behavior are encoded in the genome is not known.

The regional specificity of brain-gene relations could be parsimoniously explained by modularity (Bertolero, Yeo, Yeo, D'Esposito, & D'Esposito, 2015; Yeo et al., 2015; 2011). Despite some pleiotropy, genotype-phenotype relationships are typically modular: a single phenotype is determined by a group of genes (Wagner & Zhang, 2011; Wagner, Pavlicev, & Cheverud, 2007). In the brain, the function of regions characterized by high coexpression among a subset of genes is thought to be controlled by the same transcriptional regulatory program (Bhattacharyya, Kalita, & Roy, 2014; Oldham, Horvath, & Geschwind, 2006; van Dam, Võsa, van der

Graaf, Franke, & de Magalhães, 2017). Moreover, variation in those genes in the form of single-nucleotide polymorphisms is associated with regional variance in functional connectivity (Richiardi et al., 2015). These observations motivate the following question: Is the fact that certain genes are coexpressed in a manner that correlates with functional connectivity tantamount to the statement that brain connectivity in encoded in the genome? If so, then does the degree to which gene coexpression correlates with a particular region's connectivity reflect the amount of genetic control that is exerted over the region's function?

Here, we address these open questions in a multimodal study combining gene expression from six post-mortem brains with brain connectivity (functional and structural) and neuropsychological test scores from 1200 healthy young adults and from 914 youth between the ages of 8 and 22 yr. We begin by determining how much variance in a region's connectivity can be accounted for by gene coexpression (genetic fit), including which sets of genes maximize each region's genetic fit. We use this data to test the hypothesis that different sets of genes account for the different roles that regions play within the brain's modular network structure. We next determine the relation between genetic fits to the region's role in the network and how predictive a region's connectivity is of behavior on cognitively demanding tasks. We use this data to test the hypothesis that functional, but not structural connectivity mediates between genotypes and cognitive phenotypes, a notion supported by prior evidence of functional connectivity providing an individual fingerprint (Finn et al., 2015). Next, we determine whether and to what degree a region's connectivity is heritable to test the hypotheses that (i) functional connectivity should be more heritable than structural connectivity, and (ii) regions with high heritability are less genetically codified, and *visa versa*. Then, using the developmental sample, we determine how regional connectivity develops during adolescence to show that functional, but not structural, connectivity of nodes with the highest genetic fits have a particular developmental trajectory. We conclude with an ontology analysis of the genes involved in coding brain connectivity.

We find that gene coexpression is more strongly related to functional connectivity than to structural connectivity. Brain regions whose connections are well fit by gene coexpression also tend to have connections whose strengths are commonly shared across humans, co-vary with behavior, and display stereotyped development over adolescence. In contrast, brain regions whose connections are not well fit by gene coexpression tend to connect diverse functional network modules and be strongly heritable. Our results lend support to the notion that functional connectivity is modularly encoded in the genome and mediates between genotypes and cognitive phenotypes.

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