Genetic variance in resting-state functional connectivity

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Abstract:

Resting-state functional connectivity is a promising trait for the study of neurological disorders, behavior and cognition. These variables are better conceptualized as quantitative traits and are generally known to be influenced by a large number of genetic factors (Plomin et al., 2009; Turkheimer, 2000). Therefore, the quantitative genetic analysis of functional connectivity is a necessary first step in linking genes, connectivity and neurobehavioral disorders. In this talk, I will first introduce the basic methods of quantitative genetic analysis. The impact of genetic variation on individual differences in functional connectivity in the general population will then be presented. Lastly, methods to link genetic influences on functional connectivity to specific behavioral and disease-related traits will be discussed.

The study involved 680 healthy subjects from extended pedigrees of the GOBS study (Olvera et al., 2011). The subjects had a mean age of 42±15 years, ranging from 18 to 85 years old and 414 of the participants were women. All participants provided written informed consent and the study was approved by institutional review boards at UTHSCSA, Yale U. and McGill U. The imaging data was acquired on a Siemens 3T Trio scanner and included TurboFlash T1 images and resting-state fMRI data (Glahn et al., 2010). The structural data were processed using the CIVET software (http://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET) and the functional data were processed using the NIAK toolbox (https://www.nitrc.org/projects/niak/). Quantitative genetic analyses we carried out using the SOLAR software (Almasy and Blangero, 1998). Where applicable, corrections for multiple comparisons were done using the FDR method (Benjamini and Hochberg, 2000).

We show that genetic variance is ubiquitous throughout the connectome, but its relative contribution varies across networks. For instance, primary sensory areas along with the cerebellum tend to exhibit lower estimates and a smaller proportion of heritable connections. Conversely, frontal areas tend to exhibit higher estimates and a greater number of heritable connections. Overall, the highest estimates of heritability in the connectome were found in connections linking frontal cortices to parietal and sensorimotor areas. This mapping of genetic influences on functional connectivity is a tool that can be used both to explore the functional connectome and to guide investigations into the genetic underpinnings of behavioral and disease-related traits.

Such results must be discussed with care, however, as there are many pitfalls in the interpretation of heritability (Visscher et al., 2008). These pitfalls will be discussed, along with methods to link the results observed here to specific behavioral and disease-related traits. One interesting prospect for future studies is to use functional connectivity as an endophenotype for the identification of specific genes influencing these traits.