Estimating the Heritability of Structural and Functional Brain Connectivity in Families Affected by Attention-Deficit/Hyperactivity Disorder

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Abstract

Importance
Despite its high heritability, few risk genes have been identified for attention-deficit/hyperactivity disorder (ADHD). Brain-based phenotypes could aid gene discovery. There is a myriad of structural and functional connections that support cognition. Disruption of such connectivity is a key pathophysiologic mechanism for ADHD, and identifying heritable phenotypes within these connections could provide candidates for genomic studies.

Objective
To identify the structural and functional connections that are heritable and pertinent to ADHD.

Design, Setting, and Participants
Members of extended multigenerational families enriched for ADHD were evaluated. Structural connectivity was defined by diffusion tensor imaging (DTI) of white matter tract microstructure and functional connectivity through resting-state functional magnetic resonance imaging (rsfMRI). Heritability and association with ADHD symptoms were estimated in 24 extended multigenerational families enriched for ADHD (305 members with clinical phenotyping, 213 with DTI, and 193 with rsfMRI data). Findings were confirmed in 52 nuclear families (132 members with clinical phenotypes, 119 with DTI, and 84 with rsfMRI). The study and data analysis were conducted from April 1, 2010, to September 1, 2016.

Results
In the 52 nuclear families, 86 individuals (65.2%) were male and the mean (SD) age at imaging was 20.9 (15.0) years; in the 24 multigenerational extended families, 145 individuals (47.5%) were male and mean age at imaging was 30.4 (19.7) years. Microstructural properties of white matter tracts connecting ipsilateral cortical regions and the corpus callosum were significantly heritable, ranging from total additive genetic heritability ($h^2 = 0.69$ (SE, 0.13; $P = .0000002$) for radial diffusivity of the right superior longitudinal fasciculus to $h^2 = 0.46$ (SE, 0.15; $P = .0009$) for fractional anisotropy of the right inferior fronto-occipital fasciculus. Association with ADHD symptoms was found in several tracts, most strongly for the right superior longitudinal fasciculus ($t = -3.05$; $P = .003$). Heritable patterns of functional connectivity were detected within the default mode ($h^2 = 0.36$; SE, 0.16; cluster level significance, $P < .002$), cognitive control ($h^2 = 0.32$; SE, 0.15; $P < .002$), and ventral attention networks ($h^2 = 0.36$; SE, 0.16; $P < .002$). In all cases, subregions within each network showed heritable functional connectivity with the rest of that network. More symptoms of hyperactivity/impulsivity ($t = -2.63$; $P = .008$) and inattention ($t = -2.34$; $P = .02$) were associated with decreased functional connectivity within the default mode network. Some cross-modal correlations were purely phenotypic, such as that between axial diffusivity of the right superior longitudinal fasciculus and heritable aspects of the default mode network (phenotypic correlation, $p_p = -0.12$; $P = .03$). A genetic cross-modal correlation was seen between the ventral attention network and radial diffusivity of the right inferior fronto-occipital fasciculus (genetic correlation, $g_g = -0.45$, $P = .02$).

Conclusions
Analysis of data on multigenerational extended and nuclear families identified the features of structural and functional connectivity that are both significantly heritable and associated with ADHD. In addition, shared genetic factors account for some phenotypic correlations between functional and structural connections. Such work helps to prioritize the facets of the brain’s connectivity for future genomic studies.