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Genetic influences on cognitive endophenotypes in schizophrenia

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ABSTRACT

Background: Cognitive deficits are prominent in schizophrenia and represent promising endophenotypes for genetic research.
Methods: The current study investigated the importance of two conceptually distinct genetic aggregates, one based on copy number variations (uncommon deletion burden), and one based on single nucleotide polymorphisms identified in recent risk studies (genetic risk score). The impact of these genetic factors, and their interaction, was examined on cognitive endophenotypes defined by principal component analysis (PCA) in a multicenter sample of 50 patients with schizophrenia and 86 controls. PCA was used to identify three different types of executive function (EF: planning, fluency, and inhibition), and in separate analyses, a measure general cognitive ability (GCA).
Results: Cognitive deficits were prominent among individuals with schizophrenia, but no group differences were evident for either genetic factor. Among patients the deletion burden measures predicted cognitive deficits across the three EF components and GCA. Further, an interaction was noted between the two genetic factors for both EF and GCA and the observed patterns of interaction suggested antagonistic epistasis. In general, the set of genetic interactions examined predicted a substantial portion of variance in these cognitive endophenotypes.
Limitations: Though adequately powered, our sample size is small for a genetic study.
Conclusions: These results draw attention to genetic interactions and the possibility that genetic influences on cognition differ in patients and controls.

1. Introduction

In the search for the genetic roots of schizophrenia, the attempt to identify specific genetic influences on endophenotypes is increasingly common (Cannon and Keller, 2006). Cognitive endophenotypes such as general cognitive ability (GCA, or "g") and executive function (EF), are (1) well measured, (2) clinically relevant, (3) heritable, and (4) from a cognitive neuroscience perspective, relatively well characterized (Langer et al., 2012; Miyake and Friedman, 2012). Greenwood et al. (2013) explored genetic influences on several endophenotypes, including cognitive measures such as the California Verbal Learning Test and the Wisconsin Card Sorting Test. Linkage analysis across 296 families was unable to identify any single nucleotide polymorphism that significantly predicted performance on these cognitive tasks.

In the current report we investigate the genetic influences on GCA and EF, quantified through principal component analyses of many test scores, allowing reliable assessment of the relevant latent constructs while minimizing test-specific method variance (see Green

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et al., 2013; Gold and Dickinson, 2013, for a recent discussion of GCA in schizophrenia). Genetic influences were represented by two conceptually distinct aggregate scores, not individual genetic loci. One aggregate was based on copy number variations (CNVs) and one was based on previously identified single nucleotide polymorphisms (SNPs). CNVs may represent either deletions or duplications of segments of DNA, and collectively, they account for many times more genetic variation in nucleotide sequences than SNPs (Girirajan et al., 2011). Because deletions are under greater negative selection pressure than duplications, and the population frequency of deletions is generally inversely related to their potential for harm (Zhang et al., 2009), one simple way to represent mutation load is by the total number of rare or uncommon deletions. We reported that a greater overall burden of uncommon deletions (less than 3% frequency) predicted lower GCA in patients with schizophrenia, but not controls (Yeo et al., 2013). The specific deletions captured in this overall measure differ across individuals, constraining theoretical interpretations. The SNP aggregate used in the current study (genetic risk score, GRS), originally reported in Walton et al. (2013), was derived from the empirical literature on alleles possibly distinguishing individuals with schizophrenia from controls. This measure combined the additive effects of 41 single nucleotide polymorphisms (SNPs) in 34 genes weighted by their odds ratios. The genes involved span many functions, most prominently, neurotransmission (32%) and neurodevelopment (26%).

As cognitive skills are typically conceptualized as hierarchical in nature (McGrew, 2009), with GCA at the apex and more specific skills such as EF as lower-order components, EF and GCA covary. EF can thus be represented as either a correlated trait sharing variance with GCA, or if GCA is covaried out, as an independent cognitive ability. Analyses were conducted both ways. Thus, the current report extends our prior study of uncommon deletion burden and GCA (Yeo et al., 2013), to investigate deletion burden and GRS effects on both GCA and EF components.

2. Methods

2.1. Participants

Participants were recruited through the Mind Clinical Imaging Consortium (MCIC). This includes IRB approved research teams at the Mind Research Network and University of New Mexico, Massachusetts General Hospital, the University of Minnesota, and the University of Iowa (see Gollub et al., 2013, for additional details). From the original sample we included all participants who had high quality genetic data, structural MRI scans, and complete neuropsychological testing. The current analysis is limited to the subset of these individuals who stated that their racial background was “white”. (See Liu et al., 2012, for additional details on the issue of population stratification in the MCIC sample.) The final sample included 50 individuals with schizophrenia (35 males, 15 females) and 86 controls (49 males, 37 females). The number of participants recruited from each site was: Albuquerque, NM (11 patients/15 controls), Boston, MA (12/11), Minneapolis, MN (9/14), and Iowa City, IA (18/46).

A comprehensive clinical diagnostic assessment included either the Structured Clinical Interview for the DSM IV (First et al., 1997) or the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992). Symptoms were evaluated with the Scale for the Assessment of Positive Symptoms (Andreasen, 1984a) and the Scale for the Assessment of Negative Symptoms (Andreasen, 1984b). Healthy controls were recruited from the general community through medical clinics and advertisements in local newspapers. Exclusionary criteria for the control group were presence of a physical or neurologic disorder affecting brain function, and lifetime history of any Axis I disorder, including substance abuse or dependence. Parental socio-economic status (pSES) was calculated using the modified five-point Hollingshead–Redlich scale (1 = highest, 5 = lowest).

2.2. Cognitive assessment

Executive skills were assessed with a battery of six tests, yielding a total of 10 variables, and principal component analysis was used to reduce these variables to a smaller number of EF factors. Verbal fluency was assessed with the letter fluency (letters F, A, and S) and category fluency tests (animals and fruits) from the Delis–Kaplan Executive Functional System (Delis et al., 2001). Both total time and number of errors on the Trail Making Test B, a measure of processing speed, working memory, and sequencing, were also assessed. A computerized version of the Tower of London test was administered to assess planning and problem solving (Shallice, 1982). Three variables from this test were used: excess moves on the 3, 4, and 5 ring problems. The California Computerized Assessment Package (CalCap) taps processing speed, attention and executive skills (LaPointe et al., 2007). We included false positive errors from the Serial Pattern Matching 1 and Serial Pattern Matching 2 subtests.

A principal component analysis (PCA) with oblimin rotation (which allows for the emergence of correlated factors) was performed on the 10 executive function variables, from participants of both groups, to determine a smaller number of latent factors. This analysis was performed on the full sample (N = 237) described in Yeo et al. (2014), some of whom did not have genetic data, allowing for the emergence of a maximally stable factor structure. Given the pattern of results obtained, a follow-up analysis examined “overall EF”, which was determined by simply averaging the three components emerging from the original PCA; this overall measure correlated with a simple unweighted aggregrate of all EF variables at r = .99. GCA was operationally defined as the first component emerging from a principal component analysis of 25 variables from a comprehensive neuropsychological battery that included EF measures (Sponheim et al., 2010). The psychometric characteristics of the first principal component are quite robust to variations in the exact tests included in the PCA, as PCAs based on entirely different test correlate at r = .99 or better (Johnson et al., 2004), and in our sample, an unweighted composite of all cognitive tests employed correlated with the GCA derived from PCA at r = .99.

2.3. Genetic analyses

Details on the deletion burden measure, based on the number of uncommon deletions, were previously described (Yeo et al., 2013) and details on the GRS were provided in Walton et al. (2013). DNA extracted from blood samples was genotyped using Illumina HumanOmin1-quad chip, including 1,140,419 markers. The number of uncommon deletions (i.e., those that occurred in 3% or fewer subjects in the combined sample with high quality CNV data) was summed for each subject. SNPs for the GRS were selected based on the continuously updated meta-analysis of genetic studies on schizophrenia, available at www.schizophreniaresearchforum.org as described in Walton et al. (2013). The GRS was weighted by multiplying the number of risk alleles with the logarithmized odds ratio of each SNP to take different effect sizes of SNPs into account.

2.4. Statistical analysis

All statistical analyses were conducted in SPSS (v.21.0). A repeated measures ANOVA was performed, treating the three EF variables as repeated measures, with group as a between subjects factor and deletion burden and GRS as quantitative predictors, along with several covariates (age, sex, ethnicity [Anglo vs. Hispanic], and pSES) often found to influence cognitive scores. The repeated measures analysis allowed us to evaluate whether genetic effects were specific to a given component or generalized across all EF components. A follow-up analysis additionally covaried GCA. For our primary GCA analysis, a univariate general linear model was conducted, with the same set of factors and covariates