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Novel gene-brain structure relationships in psychotic disorder revealed using parallel independent component analyses

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ABSTRACT

Background: Schizophrenia, schizoaffective disorder, and psychotic bipolar disorder overlap with regard to symptoms, structural and functional brain abnormalities, and genetic risk factors. Neurobiological pathways connecting genes to clinical phenotypes across the spectrum from schizophrenia to psychotic bipolar disorder remain largely unknown.

Methods: We examined the relationship between structural brain changes and risk alleles across the psychosis spectrum in the multi-site Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) cohort. Regional MRI brain volumes were examined in 389 subjects with a psychotic disorder (139 schizophrenia, 90 schizoaffective disorder, and 160 psychotic bipolar disorder) and 123 healthy controls. 451,701 single-nucleotide polymorphisms were screened and processed using parallel independent component analysis (para-ICA) to assess associations between genes and structural brain abnormalities in probands.

Results: 482 subjects were included after quality control (364 individuals with psychotic disorder and 118 healthy controls). Para-ICA identified four genetic components including several risk genes already known to contribute to schizophrenia and bipolar disorder and revealed three structural components that showed overlapping relationships with the disease risk genes across the three psychotic disorders. Functional ontologies representing these gene clusters included physiological pathways involved in brain development, synaptic transmission, and ion channel activity.

Conclusions: Heritable brain structural findings such as reduced cortical thickness and surface area in probands across the psychosis spectrum were associated with somewhat distinct genes related to putative disease pathways implicated in psychotic disorders. This suggests that brain structural alterations might represent discrete psychosis intermediate phenotypes along common neurobiological pathways underlying disease expression across the psychosis spectrum.

1. Introduction

The etiopathology of psychotic disorders ranging from schizophrenia (SZ) through schizoaffective disorder (SAD) to psychotic bipolar

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disorder (PBP) is being increasingly clarified with the identification of specific putative genes and the characterization of a range of structural and functional brain abnormalities (Keshavan et al., 2008; PGC Consortium et al., 2014; Tandon et al., 2008). Large-scale genomic studies, including genome-wide association studies, have begun to implicate a number of common as well as unique loci and polymorphisms in SZ and PBP (Gatt et al., 2015). Several gene variants that underlie brain development, immune mechanisms, synaptic function and ion channels have been identified (Gratten et al., 2014). Structural brain abnormalities in SZ include gray matter volume reductions in several brain regions notably frontal and temporal cortex and subcortical regions such as hippocampus, thalamus and basal ganglia (Keshavan et al., 2008). Despite delineation of a range of neurobiological findings in patients with these conditions (Ellison-Wright et al., 2010; McDonald et al., 2006; Palaniyappan et al., 2012), their functional characterization is poorly defined and the specific pathways from etiology through pathology to clinical expression remain largely unidentified (Keshavan et al., 2011a, b).

Investigation of disease risk-related, heritable phenotypes (i.e. endophenotypes) such as neuroanatomical alterations can serve as a foot-hold in discerning the neurobiological pathways connecting genes to clinical phenotypes across the psychosis spectrum (Gottesman and Gould, 2003; Glahn, et al., 2014; Insel and Cuthbert, 2009). Structural brain abnormalities in psychotic disorders include gray matter volume reductions in several brain regions notably the frontal and temporal cortex and subcortical regions such as the hippocampus, thalamus and basal ganglia, and may serve as potential endophenotypes (Keshavan et al., 2008). However, a significant barrier to an improved understanding of the nature of various psychotic disorders is our current symptom-based nosological system which does not reliably separate biologically distinct categories and thus "does not carve nature at its joints" (Kapur et al., 2012). Although SZ, SAD, and PBP have been considered distinct clinical entities for almost a century (Kraepelin, 1919; Tandon R, 2008), there are several overlaps in disease risk genes, structural and functional intermediate phenotypes, and symptomatology and the boundaries between these diagnoses have increasingly been called into question (Hyman, 2010).

A dimensional approach examining neurobiological alterations and their genetic underpinnings agnostic to diagnosis is more likely to identify valid disease processes across the spectrum of psychotic disorders (Keshavan et al., 2011a, b). The Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) is a multi-site research collaboration established to delineate pathophysiological pathways in psychotic disorders. It focuses on examining the manifestation and distribution of a range of informative endophenotypes across the psychosis spectrum (spanning SZ, SAD, and PBP) and evaluating their genetic associations (Hill et al., 2013; Ivleva et al., 2013; Tamminga et al., 2013).

Challenges posed by limitations to processing multidimensional data are inherent in the endeavor to define pathways across domains. Specifically, discovery of multiple genes contributing to these molecular biological processes is a challenge with traditional univariate methods. In order to evaluate relationships between interacting disease risk genes and structural brain findings across psychotic disorders, one can utilize novel multivariate data-driven statistical techniques that allow simultaneous analysis of multiple modalities. One such approach is parallel independent component analysis (para-ICA) (Chen et al., 2012; Liu et al., 2008; Sui et al., 2011). Unlike univariate studies such as GWAS, para-ICA identifies linearly interacting risk gene variants, which taken together contribute to a quantitative trait, and when taken together may elucidate illness-associated molecular/biological pathways (Meda et al., 2014; Pearlson et al., 2015). The selection of a proper endophenotype is also critical, and a chief assumption in the selection of the endophenotype is that its biological pathways will be relatively closer to the action of the genes (Gottesman and Gould, 2003; Insel and Cuthbert, 2009). We addressed this by using cortical thickness and cortical surface area, measures demonstrated to be independently heritable of each other and likely to be more proximal to genetic action compared to volumetric measures commonly used in previous studies (Panizzon et al., 2009).

In this study, we applied this approach to investigate gene-brain structure relationships in patients with schizophrenia, schizoaffective disorder, and psychotic bipolar disorder. Beginning with genetic and structural brain data (single nucleotide polymorphisms [SNPs] and MRI-derived regional brain measures, respectively), we employed para-ICA to uncover underlying factors from both modalities and their relationships across psychotic disorders. We aimed to examine the association between structural components and risk genes across the psychosis spectrum (agnostic to categorical DSM diagnosis) from probands with SZ, SAD, PBP, and in healthy controls all enrolled in B-SNIP in order to determine their candidacy as potential intermediate/endophenotypes in biologically interactive disease pathways. We hypothesized that: a) we would observe structural differences such as altered cortical thickness and surface area in psychosis probands versus healthy controls, and b) that such alterations would be differentially associated with sets of genes that govern synaptic function, brain development, neuronal ion channels, and inflammatory processes previously known to be associated with psychosis risk.

2. Materials and methods

2.1. Study participants

Data were derived from the B-SNIP database on 512 subjects: 389 subjects with a psychotic disorder (139 schizophrenias, 90 schizoaffective disorders, and 160 psychotic bipolar disorders) and 123 healthy controls; 248 males, 264 females. These data included 3.0 Tesla structural MRI scans, Illumina SNP genotyping data (http://www.illumina.com; Li et al., 2008a, b, and clinical/demographic information. The institutional review boards at each of the six B-SNIP sites (Chicago, Hartford, Dallas, Detroit, Maryland and Boston) approved the study and all participants provided written informed consent. Inclusion criteria for subjects were based on a diagnosis of schizophrenia, schizoaffective disorder, psychotic bipolar disorder, or healthy controls confirmed by the Structured Clinical Interview for DSM-IV Disorders (Endris et al., 2002; First et al., 2002).

2.2. Single nucleotide polymorphism (SNP) genotype data collection and preprocessing

For all subjects for whom genotyping and morphometric data were available (N = 512), we extracted DNA from a blood sample and processed single nucleotide polymorphisms (SNPs) on an Illumina Infinium HumanOmni1-Quad microarray assay (http://www.illumina.com) covering 1,140,419 SNP loci at Genomas (Hartford, CT).

SNP genotype data underwent two pre-processing stages. We first applied a series of standard quality control measures developed to remove DNA samples and markers that might introduce bias in case-control studies (Anderson et al., 2010). Genotype data were preprocessed in PLINK (Purcell et al., 2007) following a published workflow reported by Anderson et al. (2010), combining both per-individual and per-marker quality control (see Supplementary Fig. 1). In this manner, we excluded individuals with discordant gender information, elevated missing data rates, outlying heterozygosity rates, and those who were duplicated or related. We applied thresholds for minor allele frequency of 1% and a Hardy-Weinberg equilibrium p value of 0.00001. 451,701 SNPs for 482 subjects passed quality control and were carried over to the next processing stage. SNPs in high linkage disequilibrium (LD) were first removed (window 50 SNPs, $r^2 > 0.5$) to increase independence between markers. Genotype data were then subjected to a principal component analysis (PCA) using custom Matlab scripts (Mathworks, Natick, MA) to identify stratifying factors using an algorithm similar to EIGENSTRAT (Price et al., 2006). Data were adjusted

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