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Genome-Wide Significant Linkage of Schizophrenia-Related Neuroanatomical Trait to 12q24

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The insula and medial prefrontal cortex (mPFC) share functional, histological, transcriptional, and developmental characteristics, and they serve higher cognitive functions of theoretical relevance to schizophrenia and related disorders. Meta-analyses and multivariate analysis of structural magnetic resonance imaging (MRI) scans indicate that gray matter density and volume reductions in schizophrenia are the most consistent and pronounced in a network primarily composed of the insula and mPFC. We used source-based morphometry, a multivariate technique optimized for structural MRI, in a large sample of randomly ascertained pedigrees (N = 887) to derive an insula–mPFC component and to investigate its genetic determinants. Firstly, we replicated the insula–mPFC gray matter component as an independent source of gray matter variation in the general population, and verified its relevance to schizophrenia in an

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independent case-control sample. Secondly, we showed that the neuroanatomical variation defined by this component is largely determined by additive genetic variation ($h^2 = 0.59$), and genome-wide linkage analysis resulted in a significant linkage peak at 12q24 (LOD = 3.76). This region has been of significant interest to psychiatric genetics as it contains the Darier's disease locus and other proposed susceptibility genes (e.g., *DAO*, *NOS1*), and it has been linked to affective disorders and schizophrenia in multiple populations. Thus, in conjunction with previous clinical studies, our data imply that one or more psychiatric risk variants at 12q24 are co-inherited with reductions in mPFC and insula gray matter concentration.

Key words: extended pedigrees; magnetic resonance imaging; insula; medial prefrontal cortex; quantitative trait locus

INTRODUCTION

Schizophrenia is a heritable disorder [Sullivan et al., 2003] but the genetic variation accounting for its inheritance is complex and difficult to characterize. Many genetic markers, both common and rare, are thought to contribute to genetic risk for schizophrenia and related disorders [Gratten et al., 2014]. Efforts to localize susceptibility variants and investigate their downstream effects on protein synthesis and interactions are hindered by the heterogeneity and complexity of the clinical phenotype, and by the small effect sizes of the common variants typically identified by large-scale association studies. Family-based designs offer increased power to identify genetic variants, especially rare variants with potentially larger effect sizes [Williams and Blangero, 1999]. In addition, intermediate phenotypes that are heritable and genetically associated with a clinical diagnosis can facilitate variant localization, both because of their quantitative nature and because of their assumed proximity to the genetic effects [Glahn et al., 2007; Gottesman and Gould, 2003]. Simultaneously, these endophenotypes [Gottesman and Gould, 2003] provide insights into the variants' influences on biological processes, yielding clues to pathological mechanisms that contribute to the expression of the clinical phenotype.

Neuroanatomical traits derived from magnetic resonance imaging (MRI) are logical endophenotypes as their selection can be informed by a large body of the literature in clinical samples, and they are likely to be biologically intermediate between genes' functions and their more remote effects on behavioral phenotypes [Glahn et al., 2007]. Despite marked clinical and methodological heterogeneity, multiple meta-analyses of voxel-based morphometry studies in schizophrenia have identified the insula and the medial prefrontal cortex (mPFC) as the neuroanatomical regions most consistently associated with schizophrenia across all published case-control studies [Glahn et al., 2008; Fornito et al., 2009; Bora et al., 2011; Palaniyappan et al., 2012; Shepherd et al., 2012].

Source-based morphometry (SBM) [Xu et al., 2009] is a multivariate method that decomposes gray matter concentration images, derived from T_1-weighted MRI scans, into spatially independent sources. The outcome is a matrix of weights for each individual on each source map, which can be used as dependent variables instead of voxel-wise values. As such, SBM dramatically reduces the number of comparisons typically performed in voxel-based analyses. SBM also addresses other common problems in MRI analysis, including the choice of smoothness kernel and the non-stationarity of image smoothness [Hayasaka and Nichols, 2003]. Remarkably, the application of SBM has repeatedly identified a single component comprising the mPFC and the insula—the same regions as the case-control meta-analyses (15–19)—as the most affected anatomical network in schizophrenia patients [Gupta et al., 2015; Xu et al., 2009; Kasparek et al., 2010; Turner et al., 2012]. Thus, following an endophenotype strategy, quantification and localization of the genetic influences on this schizophrenia-associated neuroanatomical trait could provide testable candidate genes and generate novel hypotheses about mechanisms underlying susceptibility for schizophrenia.

Here, we used SBM in a large sample of randomly ascertained pedigrees. Our aims were threefold: (i) to replicate the schizophrenia-associated insula–mPFC source as a spatially independent component in a new sample representative of the general population; (ii) to estimate its heritability; and (iii) to localize this genetic influence to specific genomic regions using linkage analysis.

MATERIALS AND METHODS

GOBS Extended Pedigree Sample

Participants were individuals of Mexican American ancestry who took part in the genetics of brain structure and function study (GOBS) [Olvera et al., 2011; McKay et al., 2014], which is an extension of the San Antonio family study [Mitchell et al., 1996]. Individuals were randomly selected from the community with the only constraints that they were part of a large family of Mexican–American ancestry and lived within the San Antonio region. For the present analysis, subjects were excluded for MRI contraindications, documented medical history of neurological illness, or any neurological event visible on the T_1-weighted scans (see Source-Based Morphometry Section). Of the participants in the final analysis, 22 self-reported history of a neurological event or illness (18 stroke, 1 Parkinson's disease, 3 multiple sclerosis, 1 brain surgery), but excluding these individuals did not change the pattern of results presented. After quality control procedures (see below), T_1-weighted scans were available for 887 individuals (532 female), from 69 pedigrees ranging from 2 to 90 family members, and 46 singletons. Participants were between 18 and 85 years old (mean = 44; standard deviation (SD) = 15).

History of axis-1 disorders was assessed using the Mini-International Neuropsychiatric Interview [Sheehan et al., 1998]. Of the individuals included in the main analysis, four had a diagnosis of schizophrenia, 15 of bipolar disorder, and four of schizoaffective disorder. For our main results, we performed additional analyses excluding these individuals (see Results Section). Additionally, 297 participants had a history of major depression, and 118 had a history of an anxiety disorder, and we performed additional analyses co-varying for these diagnoses.

MR Imaging and Processing in GOBS

An MRI protocol optimized for cortical gray matter measurements [Kochunov and Davis, 2009], with a retrospective motion correction technique [Kochunov et al., 2006], was used. For each participant, seven T_1-weighted scans were obtained in a Siemens 3 Tesla Trio scanner located at the Research Imaging Institute, University of Texas Health Science Center, using a magnetization prepared sequence with an adiabatic inversion contrast-forming pulse (scan parameters: TE/TR/TI = 3.04/2100/785 ms, flip angle = 11°). As in Kochunov et al. [2006], for each subject, the seven volumes were co-registered and averaged.

Upon visual inspection, five individuals were excluded for neurological abnormalities, and one for a scanner artifact. The resulting images were further processed in SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/), using the same parameters as in Turner et al. [Gupta et al., 2015; Turner et al., 2012] and Xu et al. [2009]. Gray matter maps were non-linearly normalized, resliced to a 2 mm^3 MNI template, and segmented into gray matter, white matter, and cerebrospinal fluid [Ashburner and Friston, 2000]. The accuracy of the segmentations and normalizations was ensured by visual inspection and by calculating correlations with the average normalized gray matter map for the entire sample. Five individuals were excluded because of segmentation or normalization problems.

Source-Based Morphometry

SBM [Xu et al., 2009; Kasparek et al., 2010] (http://mialab.mrn.org/software/gift/) is a multivariate method that decomposes structural images into spatially distinct sources using independent component analysis [Bell and Sejnowski, 1995]. The decomposition of the subject-by-voxel matrix (X) results in a subject-by-component mixing matrix (W), which contains the weights of the subjects on each component; and a component-by-voxel source matrix (C), which contains the loadings of each voxel for each component. This decomposition[1] can be noted as follows [Calhoun et al., 2001]:

$$X = W*C$$

And, therefore,

$$W = X*C^{-1}$$

For a subject i, the weight of a component j reflects the overall gray matter concentration for that component map of n voxels. More quantitatively, the weight can be conceived of as the sum of each voxel's observed gray matter value multiplied by each voxel's loading on the component:

$$W_{i,j} = \sum_{k=1}^{n} X_{i,k} C_{k,j}^{-1}$$

These weights can be used as dependent variables in subsequent analyses.

The optimal number of components for our data was estimated according to an information criteria algorithm [Li et al., 2007]. To determine the stability of the decomposition, ICASSO [Himberg et al., 2004] was used, with random value initiation and bootstrapping options, for 20 repetitions.[2] The stability indices for all components were higher than 0.97.

Relevance to Schizophrenia: Application to an Independent Case-Control Cohort

While we had strong a priori evidence for the involvement of insula and mPFC gray matter in schizophrenia [Glahn et al., 2008; Fornito et al., 2009; Bora et al., 2011; Palaniyappan et al., 2012; Shepherd et al., 2012; Turner et al., 2012], we also directly verified the relevance of the currently derived component to brain morphology of schizophrenia in a separate dataset of 936 healthy control participants (HC) and 784 patients with schizophrenia (SCZ), aggregated from eight independent studies. More detailed information about the case-control sample are presented in the Supplementary Materials and in Gupta et al. [2015].

Using spatio-temporal regression, a method available in the SBM toolbox, we obtained weighting scores for each individual in the case-control dataset for the components identified using the GOBS data. By entering these as the dependent variable in a regression with study site, diagnosis, and their interactions as factors, we tested directly whether gray matter concentration defined by the component extracted from the GOBS dataset was reduced in patients with schizophrenia.

In addition, we quantified the similarity between the components derived from the GOBS and the case-control datasets by calculating (i) pairwise correlations of the voxel loading values across maps from both datasets; and (ii) Dice coefficients of the thresholded maps at $z > 3$, where the Dice coefficient is defined as twice the number of voxels with the same value in both maps divided by total number of voxels (within the masks).

Heritability Analysis

All quantitative genetics analyses were performed in SOLAR [Almasy and Blangero, 1998], which decomposes the variance of a trait into genetic and environmental components by modeling the covariance between individuals as a function of their genetic proximity. Typically, the trait variance is decomposed into an additive genetic effects (heritability), covariate effects (sex, age, age^2, age × sex, age^2 × sex), and residual environmental effects. We also tested for cubic effects of age, but these were negligible ($P > 0.9$) and dropped from the model. The significance of each variance component is assessed by a likelihood-ratio test

[1]In practice, this decomposition of interest is preceded by an initial principal component analysis step on the subject-by-voxel matrix X to obtain a square matrix RX, as explained in Calhoun et al. (32). For clarity, we have omitted this step from the current explanation and also note the inverse of C as C^{-1} even though it would technically be non-square if we omitted the PCA step.

[2]Note that in this case, bootstrapping is applied to estimate the degree of variability across iterations, and not—as commonly is the case—to estimate a null-distribution, which would require many more iterations.

comparing the final model to the model without the variable of interest. Using the subject's weights on the insula–mPFC component as a trait, this method yielded an index of the overall heritability (h^2) of gray matter concentration within the anatomical regions of the component. Prior to running SOLAR, eight outliers (mean $\pm$ 3$\times$SD) were removed from the data and the remaining weights were transformed using an inverse normalization transformation.

Linkage and Association Analyses

Linkage analysis was performed in SOLAR, by adding location-specific identity-by-descent (IBD) information to the above heritability model. IBD means that two individuals within the same pedigree not only share the same genotype but also inherited it from the same founder. Here, for the GOBS pedigrees, the IBD matrices were estimated as in Curran et al. [2013], using the Loki package [Heath, 1997]. In brief, for 15,000 SNPs[3] across the genome, which were selected to be in linkage equilibrium ($r < 0.2$), Loki applies Marcov Chain Monte Carlo sampling methods to empirically estimate the pairwise IBD probabilities for each SNP between each individual [Heath, 1997].

The significance of the contribution of each locus is quantified by a LOD score, defined as the logarithm (base 10) of the ratio of the likelihood of the model with the locus-specific IBD matrix to the model without this component (i.e., the same model used to test heritability). The LOD threshold for genome-wide significance was determined a priori for the complex pedigree structure of GOBS. This calculation is based on Gaussian models of the probability of crossover rates under the null distribution [Feingold et al., 1993], given our pedigree structure, the number of SNPs in our IBD matrix, and known Haldane maps. Given our pedigree structure and distribution of markers, a LOD of 2.9 is required for genome-wide significant linkage (genome-wide $\alpha < 0.05$).

To further determine whether any specific SNPs were driving the observed linkage, association analysis was performed for all common SNPs under the linkage peak (defined as all consecutive loci with LODs greater than half the maximum LOD). DNA was extracted from lymphocytes, genotyped using Illumina beadchips (Human1M-Duo Beadchip; or HumanHap550 BeadChip in tandem with HumanHap450S Beadchip), and checked for accordance with Mendelian consistency as described previously [Sprooten et al., 2014]. To account for pedigree structure, association analysis was performed in SOLAR, using methods identical to [Sprooten et al., 2014]. In brief, the minor allele dosage of each tagging SNP is added as a covariate to the model used for heritability. A corrected *P*-value was calculated according to family-wise error rate at 5%, by calculating in SOLAR the effective number of independent SNPs under the peak, adjusted for linkage disequilibrium (LD) [Moskvina and Schmidt, 2008].

[3]Note that here the SNPs are not used to test for association testing but merely to represent an independent locus for IBD estimation to perform linkage.

RESULTS

Identification and Validation of Insula-mPFC Component

The method of Li [Li et al., 2007] estimated that the GOBS gray matter images were optimally explained by 21 independent sources.

As hypothesized, one component (Fig. 1) closely resembled the insula–mPFC clusters resulting from the aforementioned voxel-based morphometry meta-analyses [Bora et al., 2011; Palaniyappan et al., 2012; Shepherd et al., 2012], as well as previous SBM studies [Gupta et al., 2015; Turner et al., 2012; Xu et al., 2009]. The bilateral insular parts of this component contained voxels in the insula and temporal pole, extending to the inferior frontal, orbitofrontal, opercular, and superior temporal gyri. The frontal cluster of the component contained voxels in the anterior cingulate and paracingulate gyrus, frontal pole, medial frontal cortex, and superior frontal gyrus. A small number of voxels were negatively correlated with the mPFC and insula, mostly containing white matter in the superior parietal lobes and splenium.

In line with qualitative comparisons to the literature, spatio-temporal regression in the case-control dataset revealed that the weights on this insula–mPFC component were highly significantly different between schizophrenia patients and healthy participants ($F = 292.69$, $P = 1.19 \times 10^{-60}$), in the absence of site-by-diagnosis interactions ($F = 1.24$, $P = 0.22$). The correlation coefficient of the loadings across voxels between this map and the map derived from the case-control data was 0.58 and the Dice coefficient was 0.97, both indicating a high degree of overlap.

The present paper focuses on the insula–mPFC cluster. We provide information about all 21 component maps including heritability estimates and case-control statistics in the Supplementary Materials.

Quantitative Trait Localization

The polygenic model in SOLAR using the weights of the insula–mPFC component as quantitative trait revealed that gray matter in this region is significantly heritable ($h^2 = 0.59$; $P = 1.78 \times 10^{-15}$). Linkage analysis resulted in a genome-wide significant peak on chromosome 12 at 12q24 (12q24.11–12q24.23; maximum LOD = 3.76; Fig. 2).

The linkage peak contained 392 tagging SNPs. Taking into account LD, the peak-wide corrected *P*-value for SNP associations was 1.64×10^{-4}. None of the SNPs were peak-wide significant (Fig. S2). The strongest association ($P = 7.71 \times 10^{-4}$) was found for rs7133582, an intronic SNP in a transcription factor binding site in *KSR2*. Several other nearby SNPs had modest to strong associations with the insula–mPFC trait, altogether spanning 12q24.21–12q24.23.

Pedigree-specific LODs were all < 1, indicating that linkage was not driven by any specific pedigree. The heritability and the linkage results remained similar when excluding individuals with self-reported history of neurological events or illness, schizophrenia, schizoaffective disorder, and bipolar disorder ($h^2 = 0.52$; LOD = 3.19) and when co-varying for history of anxiety disorders ($h^2 = 0.60$; LOD = 3.06) and major depressive disorder ($h^2 = 0.60$; LOD = 2.97). There were no significant effects of history of major

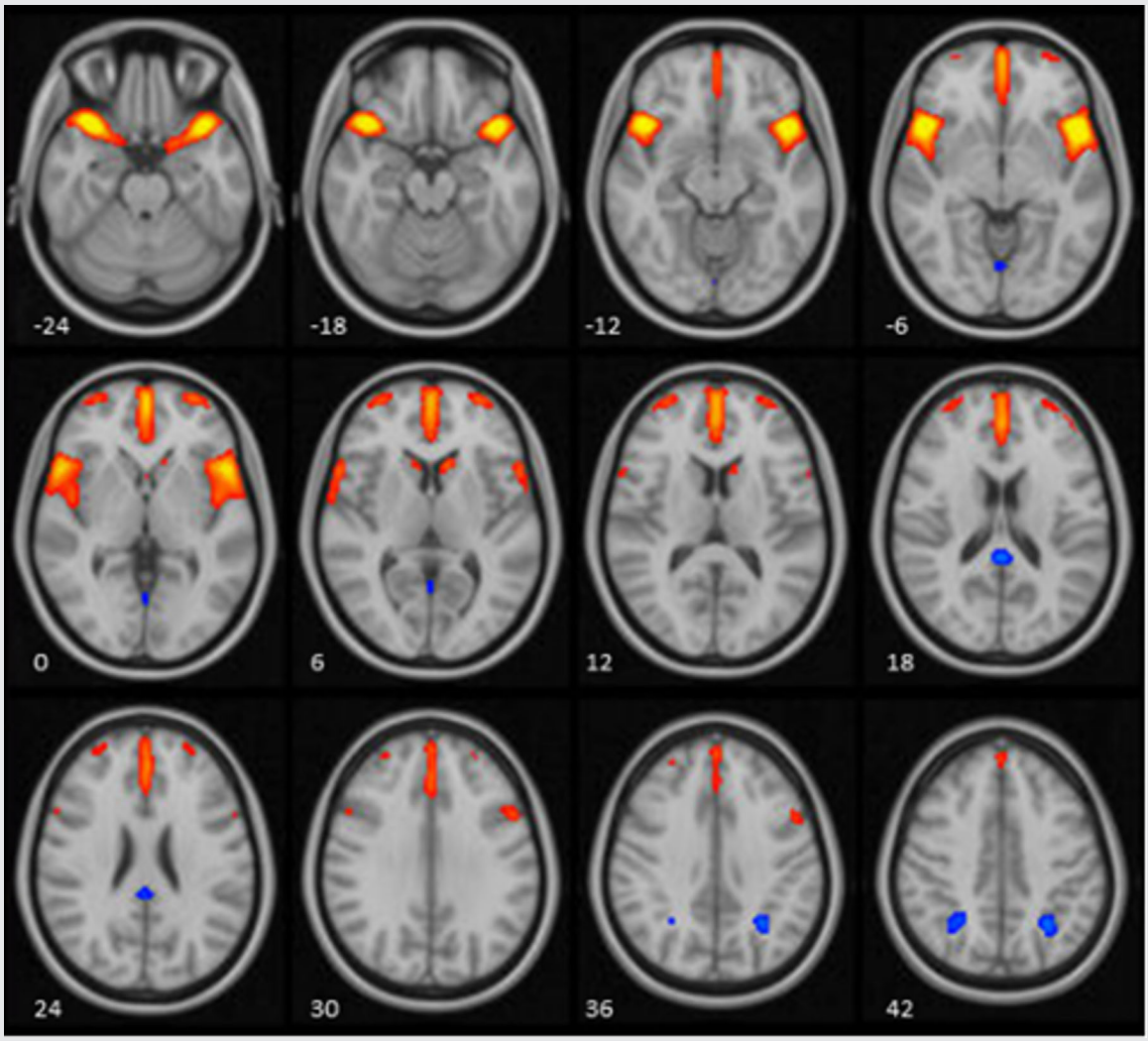

FIG. 1. The insula–mPFC component derived from SBM analysis in GOBS. Insula–mPFC component map showing the voxels that primarily contribute to the component of interest, and that covary highly with one another across individuals in the GOBS sample. Voxels loading positively ($z > 2.5$) on the component are colored red-to-yellow, and voxels loading negatively ($z < -2.5$) are colored blue-to-light blue. Images are in radiological convention. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmgb]

depression ($P > 0.8$) or anxiety disorders ($P > 0.3$) on the component's weights.

To further assess the value of the SBM approach, we also extracted gray matter concentration averages within a binarized mask of the component map ($z > 3$) for each individual. This univariate phenotype was less heritable ($h^2 = 0.47$, $P = 3.08 \times 10^{-11}$), and the maximum LOD score on chromosome 12 was found at the same marker at 12q24 as the multivariate phenotype, but was much lower (LOD = 1.82).

DISCUSSION

We used multivariate analyses of MRI images to extract a gray matter component comprising the insula and the mPFC, which have previously been shown be the most pronounced [Gupta et al., 2015; Turner et al., 2012] and most consistently implicated gray matter regions in schizophrenia [Bora et al., 2011; Fornito et al., 2009; Glahn et al., 2007; Palaniyappan et al., 2012; Shepherd et al., 2012]. We directly confirmed that gray matter defined by our empirically derived component was reduced in patients with schizophrenia from an independent case-control sample. Next, we found that the overall gray matter concentration in this component is heritable, and following genome-wide linkage analysis, we identified a quantitative trait locus for this component at 12q24.

Replication and Interpretation of Insula-mPFC Component

So far, SBM has been predominantly applied to case-control studies in schizophrenia [Gupta et al., 2015; Turner et al., 2012; Xu et al., 2009]. Together these studies investigated three independent samples, in four separate analyses, all of which

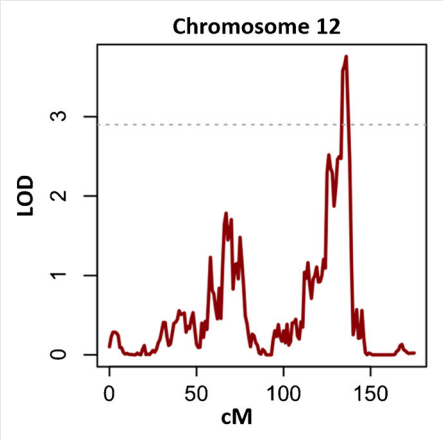

FIG. 2. Linkage peak on chromosome 12 at 12q24 for weights on the insula–medial prefrontal cortex component. LOD scores plotted against location on chromosome 12. The maximum LOD is 3.76 at 12q24. The threshold for genome-wide significance is at 2.9, as indicated by the dashed line. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmgb]

highlight the insula–mPFC component as the most important gray matter component in association with schizophrenia. The replication and heritability of this component in a sample representative of the general population supports the reliability of this technique, and indicates that gray-matter variation in this network is influenced by genetic factors.

The notion of the mPFC–insula as a coherent network is consistent with histological, anatomical, functional, and developmental similarities between these regions. The insula and the mPFC display similarly high rates of cortical thickening during neonatal development [Lyall et al., 2014] and throughout childhood [Sowell et al., 2004]. Histologically, they are also similar most notably because of the distinct and exclusive presence of von Economo neurons in these regions [Butti et al., 2013]. As key regions of the limbic system, and more specifically the "salience network" [Seeley et al., 2007], the mPFC and insula interact intensely to serve higher order cognitive processes such as social and self-awareness, intuition, error monitoring, and interoception. As such, their dysfunction has been postulated to lie at the core of the experience of psychotic symptoms [Kapur, 2003; Palaniyappan et al., 2012; Pu et al., 2012]. In a complimentary theory, interactions between superior temporal, inferior frontal regions, and the mPFC have long been hypothesized as key to the experience of auditory verbal hallucinations [Fletcher et al., 1999; Stephan et al., 2009].

Locus 12q24

We identified a 10 Mb region at 12q24 linked to the insula–mPFC gray matter phenotype. This region has been of great interest to psychiatric genetics since Craddock et al. [1994] reported a cosegregation of bipolar disorder and Darier's disease, a skin disease that is caused by mutations in *ATP2A2* [Bashir et al., 1993; Craddock et al., 1993] (Fig. S2). Subsequently, dozens of studies reported linkage of 12q24 to affective disorders in the UK, Ireland, Germany, Denmark, Canada, Iceland, and Finland in locations spanning from 12q22 to 12q24 [Jones et al., 2002; Ekholm et al., 2003; McInnis et al., 2003; Morissette et al., 1999]. Fewer but better powered studies have linked schizophrenia to 12q24 with loci mostly concentrated in 12q24.11–12q24-31 (113–128 Mb; Assembly GRCh37/hg19) [Moises et al., 1995; DeLisi et al., 2002; Williams et al., 2003; Faraone et al., 2006; Bulayeva et al., 2007; Holmans et al., 2009]. This narrowed region matches our mPFC–insula locus, as well as another linkage result in relation to neurocognitive performance in schizophrenia patients [Lien et al., 2010].

In our association study, we were unable to localize our linkage signal to any specific variants. The strongest association was found for rs7133582, a SNP in a transcription factor binding site of *KSR2*, a functionally poorly characterized gene that is involved in the MAPK and ERK signaling pathways [Dougherty et al., 2009]. Similarly, despite the considerable interest in the region, previous studies have not been able to unequivocally identify specific genes that may drive linkage results at 12q24. Although in the most recent genome-wide association analysis of schizophrenia, the Psychiatric Genomics Consortium identified a top SNP in the Darier's gene *ATP2A2* with $P < 10^{-9}$ (Schizophrenia Working Group of the Psychiatric Genomics 2014), in the original Darier's disease pedigrees risk for psychiatric disorders did not map to *ATP2A2* itself [Jacobsen et al., 2001], and the co-segregation of psychiatric symptoms with Darier's disease was thought to be due to nearby variation in LD [Jones et al., 2002]. Other efforts to identify specific neuropsychiatric risk genes at 12q24 overall yielded inconclusive results [Dawson et al., 1995; Jacobsen et al., 1996; Shink et al., 2005]. Several large-scale family studies highlight the genetic heterogeneity at 12q24 [Bulayeva et al., 2007; McInnis et al., 2003; Shink et al., 2005], and it has been suggested that the wider 12q23–12q24 region contains multiple genes that may influence neuropsychiatric phenotypes [Shink et al., 2005; Barden et al., 2006]. The original fine-mapping studies suggested CUX2, FAM109A (or FLJ32356) [Glaser et al., 2005], P2RX7, CAMKK2, [Barden et al., 2006], and LINC00944 ("Slynar gene") [Kalsi et al., 2006; Buttenschon et al., 2010]. However 12q24 also contains the schizophrenia candidate genes DAO [Verrall et al., 2010] and NOS1 [Cui et al., 2010; Silberberg et al., 2010; Wockner et al., 2014]. Interestingly, during fetal development, NOS1 is transiently highly expressed in the mPFC and insula only [Funk and Kwan, 2014], and variants in NOS1 have been associated with prefrontal morphology and function [Rose et al., 2012]. Finally, rs7294919, the genome-wide association with hippocampal volume identified by the ENIGMA and CHARGE consortia [Bis et al., 2012; Stein et al., 2012], also lies under our linkage peak.

Strengths and Limitations

An advantage of our multivariate voxel-based analysis is that it gave rise to a reliably identifiable and data-driven single trait that was known to be relevant to schizophrenia based on a large body of the pre-existing literature. However, a limitation of all voxel-based techniques is that the concentration values bear an indirect relationship to the physiological, morphological, and cellular

properties within each voxel. Both regional thickness and surface area contribute independently to voxel-wise gray matter concentrations [Winkler et al., 2010; Rimol et al., 2012], and likely local cortical curvature and white matter morphology also play a role. As such, an understanding of the biological mechanisms of the genetic effects we identified requires further specification of the morphological properties that contribute to the schizophrenia-related phenotype we investigated here.

Secondly, there is a multitude of a priori evidence and a strong rationale for the relevance of our quantitative trait to schizophrenia, which we also directly confirmed in an independent case-control dataset. However, a limitation of our study, as of most intermediate phenotype studies, is that neither endophenotype-disease associations nor quantitative genetics analyses directly test the assumption that the endophenotype lies on the causal pathway from genetic risk variants to development of disease. This is a general limitation of the field that can only truly be addressed by longitudinal designs, which are difficult to obtain to the same quantity as the data we present here, and to this date lack the statistical power and/or suitable pedigree structures for gene localization and identification.

Thirdly, while our linkage peak was not driven by any specific families within our sample, the detection of a genetic signal that is potentially obscured by locus heterogeneity (whether caused by rare or common variants) is likely facilitated by the use of a quantitative intermediate phenotype and the recruitment of large pedigrees. However, as discussed, we were unable to localize the genetic effects to any specific genes or variants. Large-scale family-based analysis of deep sequence data may be necessary to obtain more definitive answers regarding which and to what extent specific genes at 12q24 influence brain morphology and neuropsychiatric phenotypes.

Conclusions

There is compelling evidence that gray matter concentration in the insula and mPFC is reduced in patients with schizophrenia and in their unaffected family members. The genomic region 12q24 has been linked to psychiatric disorders in multiple populations worldwide and contains many genes of interest for neuropsychiatric phenotypes. Our findings indicate that genetic variation in this region also contributes to gray matter concentration in the insula and mPFC in the general population. Thus, mPFC and insula morphology are likely neuroanatomical correlates of schizophrenia that are co-inherited with schizophrenia susceptibility variants at 12q24.

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