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Multivariate Alterations in Insula - Medial Prefrontal Cortex Linked to Genetics in 12q24 in Schizophrenia

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Authors' Statement

Authors' contributions: J.T., J.L., and W.J. designed the study. W.J. analyzed the data. W.J. and K.R.M. wrote the article, which all authors reviewed. All authors approved the final version to be published and can certify that no other individuals not listed as authors have made substantial contributions to the paper.

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Abstract

The direct effect of genetic variations on clinical phenotypes within schizophrenia (SZ) remains elusive. We examined the previously identified association of reduced gray matter concentration in the insula - medial prefrontal cortex and a quantitative trait locus located in 12q24 in a SZ dataset. The main analysis was performed on 1461 SNPs and 830 participants. The highest contributing SNPs were localized in five genes including TMEM119, which encodes a microglial marker, that is associated with neuroinflammation and Alzheimer's disease. The gene set in 12q4 may partially explain brain alterations in SZ, but they may also relate to other psychiatric and developmental disorders.

Keywords

schizophrenia; QTL; insula

1. Introduction

Schizophrenia (SZ) is associated with global and regional gray matter reduction (Glahn et al., 2008; Gupta et al., 2015; Turner et al., 2012; Vita et al., 2012). The heritability of SZ is estimated to be around 70–80%, but with widespread small effects across the genome (Gejman et al., 2010; Ripke et al., 2013, 2014). Previous genome wide association studies (GWAS) have identified multiple genetic variations that may be associated with SZ risk or specific clinical phenotypes of SZ (Richards et al., 2019; Ripke et al., 2014). Even so, the identified "risk" variants for SZ from these studies of common genetic variants only explain a small proportion (up to 20%) of the variance (Eichler et al., 2010). Regardless, identification of these variations may be a helpful first-step for personalized treatments (Lee et al., 2018; Ozomaro et al., 2013). However, given the heterogenous nature of schizophrenia and the unclear genetic effects on clinical phenotypes, additional investigation is needed.

Besides the well-known gray matter reductions in the frontal lobes, insula, and hippocampus in individuals with SZ (van Erp et al., 2016, 2018), multivariate analyses, such as source-based morphometry (SBM), allow for specific brain patterns to emerge and provide a more detailed image of the phenotype of interest. In our previous SBM studies, we have identified several patterns of reduced grey matter concentration (GMC) in SZ compared to healthy controls, which were also related to familiality (Gupta et al., 2015; Sprooten et al., 2015; Turner et al., 2012). In particular, an identified pattern in the insula - medial prefrontal cortex (mPFC), has repeatedly shown a GMC reduction in individuals with SZ (Gupta et al., 2015; van Erp et al., 2018). This GMC pattern was also significantly associated with a quantitative trait locus (QTL) located at the 12q24 region in the general population (Sprooten et al., 2015). Therefore, we hypothesize that this QTL region may also relate to the insula – mPFC region in SZ. We sought to refine the gene-brain association through

a parallel independent component analysis (pICA) of correlated gray matter and genetic variants. Then, we sought to replicate those findings with an additional, independent dataset.

2. Methods

2.1 Participants

This study included 469 individuals diagnosed with SZ and 481 unrelated healthy controls from the following datasets, all previously described in the literature; the Functional imaging Biomedical Information Research Network study (FBIRN 3; multiple sites in the USA) (Potkin et al., 2009; Wible et al., 2009), the Center of Biomedical Research Excellence study (COBRE; Albuquerque, NM, USA) (Aine et al., 2017; Gupta et al., 2015), the Bipolar and Schizophrenia Network for Intermediate Phenotypes study (B-SNIP; multiple sites in the USA) (Meda et al., 2014), the Mind Clinical Imaging Consortium study (MCIC; Albuquerque, NM, USA) (Gollub et al., 2013), the Northwestern University Schizophrenia Data study (NW; Chicago, IL, USA)(Cobia et al., 2011), and the Human Brain Informatics (HUBIN; Stockholm, Sweden) (Nesvåg et al., 2008). For ease, the dataset used for this current study is referred to as the Combined dataset.

An independent cohort consisting of 182 individuals diagnosed with SZ and 351 unrelated healthy controls was used for secondary validation (The Maryland Psychiatric Research Center dataset (MPRC); Catonsville, MD, USA)(Kochunov et al., 2017). A diagnosis of SZ was confirmed by the Structured Clinical Interview for Diagnosis (SCID) for Diagnostic and Statistical Manual of Mental Health 4th Edition (DSM-IV or DSM-IV TR) as part of each study site's protocol. Participant recruitment, informed consent, and detailed participant demographics are further explained in Supplemental Appendix 1, Supplemental Tables 1, and 2.

2.2 Genetic data preprocessing

Detailed DNA sample acquiring, genotyping, imputation, pre-/post-imputation quality control, and population stratification correction information for the two datasets are provided in Supplemental Appendix 2. We extracted the 12q24 QTL region in the preprocessed genetic data. A total of 1461 overlapping single nucleotide polymorphisms (SNPs) were matched with the same minor alleles between datasets and survived pruning. The surviving SNPs were utilized for the main analyses.

2.3 Neuroimaging

T1-weighted structural MRI images were acquired from various scanners with information further detailed in Supplemental Table 1 and the original studies. The imaging preprocessing procedure was the same as in previous studies and is further detailed in Supplemental Appendix 3. In brief, a total of 830 GMC images (409 individuals with SZ and 421 healthy controls) were regressed for age, sex, and site and smoothed at 10 mm FWHM prior to analyses. The validation dataset MPRC followed the same procedure (resulting in 159 individuals with SZ and 321 healthy controls).

2.4 Association Analyses of Genetic and Structural Brain Data

Briefly, the minimum description length algorithm recommended 15 components for the genetic data and 25 components for the structural brain data (Rissanen, 1978). The associations between the QTL gene components and structural brain components were examined through pICA using the fusion ICA Toolbox (FIT; http://trendscenter.org/software/fit/). Detailed information on the pICA protocol is described in Supplemental Appendix 4.

2.5 Validation in the Independent Dataset

Following the pICA, the resulting components (both genetic and gray matter) were projected onto the above described MPRC dataset as validation. Once projected, the correlations of the components were re-analyzed. Further detail about the MPRC dataset and the validation projection can be found in Supplemental Appendix 5.

3. Results

One genetic component and one gray matter component emerged as a significant association in the combined dataset, which is shown in Figure 1b and 1a, respectively. The insula – mPFC gray matter component was negatively correlated (Figure 1c) with a genetic component involved in the QTL ($r = -0.15$, $p = 8.01E\text{-}06$ (passing Bonferroni correction)). Specifically, the specific allele was related to lower regional GMC in positive regions (z-score > 0) within the component (see Figure 1a).

These components were then projected onto the MPRC dataset for validation. The correlation between genetic and GM components remained the same direction, however, the strength was no longer significant ($r = -0.08$, $p = 0.09$) (see Figure 1d). Annotation of the highest contributing SNPs (z score ≥ |3|) within the genetic component found the following genes: WSCD2, SART3, CMKLR1, ISCU, and TMEM119 (using SNPnexus, https://www.snp-nexus.org/v4/; see Table 1 for more details).

4. Discussion

In this study, we replicated the reduced GMC in the insula – mPFC component in individuals with SZ when compared to healthy controls. These results, when taken with the previous findings (Glahn et al., 2008; Turner et al., 2012), confirm that altered insula – mPFC brain pattern is a consistent and robust finding in the SZ population. In addition, the insula – mPFC component has also appeared in the bipolar depression literature (Townsend et al., 2013), and a similar region showed reduced activation in individuals with autism during social cognition tasks (Pinkham et al., 2008). Given the negative correlation between the insula – mPFC component and the genes in 12q24 QTL, we hypothesize that the link between this identified gray matter component may be partially explained by specific genes in 12q24.

The protein-coding genes contributing to the correlated genetic component have been implicated in psychiatric disorders, immune response, and neuroinflammation. Specifically, TMEM119, encodes a protein that is involved in microglia activation during inflammation

(Wang et al., 2019) and Alzheimer's disease (Bonham et al., 2019; Satoh et al., 2016) indicating this gene as a good candidate for disease-associated risk. The WSCD2 protein is heavily involved in glucose metabolism (Postolache et al., 2019; Taneera et al., 2015) and has been associated with anxiousness in bipolar disorder (Greenwood et al., 2012) and the personality trait of extraversion (Lo et al., 2017). The 12q24 locus has also been implicated in other disorders, including bipolar depression (Green et al., 2005), autism spectrum disorder (Lin et al., 2020), and Darier's disease(Jones et al., 2002) which is associated with a high risk of bipolar depression and, to a lesser extent, schizophrenia (Cederlöf et al., 2015; Craddock et al., 1994; Jacobsen et al., 2001) [36–38]. Therefore, these genes may be related to multiple cortical dysfunctions while not specifically contributing to the development of SZ.

4.1 Limitations

A limitation of this study is the sample size, as the larger Combined ($N = 830$) and the smaller independent ($N = 471$) datasets may not be sufficient to confidently identify all SNPs. Another limitation of this study was that the ethnicity was not consistent between the original dataset and the MPRC dataset that was utilized for replication. The difference in proportions of African American participants (15% and 32%, respectively) and Hispanic participants (19% and 2%, respectively) may account for the lack of significant, yet directionally consistent, results. There was also a difference in imputation methods because of original dataset including legacy data. This limitation was controlled for using a confirmatory analysis approach that did not require combining datasets and therefore, the difference in imputation protocols did not bias the results. However, even with the heterogeneity of the ethnicities and the imputations, the association between the insula – mPFC component and the genetic component remained consistent, validating the strength of the association. A larger, yet more ethnically consistent, dataset may yield significant replication. Lastly, DOI is known to have an effect on gray matter, especially in schizophrenia studies (Tanskanen et al., 2010; van Haren et al., 2007). Although, DOI is a variable that is difficult to assess reliably and our results did not show a significant association between DOI and the insula – mPFC component, future studies would benefit from thoroughly examining the relation between DOI, gray matter, and the genetic profile in individuals with schizophrenia.

4.2 Conclusions

The findings of this study and the previous studies indicate that the insula – mPFC component is a reliable gray matter system that is affected in the SZ population. Unique to this study, we also identified SNPs that may tag plausible candidate genes associated with the brain abnormalities identified in SZ. These protein coding genes have been associated with a variety of disorders and attributes and therefore, may have a broader relation to cortical dysfunction than a specific association with SZ. The associations of these genes with bipolar depression and autism spectrum disorder should not discount the potential for insights into the genetic and structural architecture of SZ given the genetic overlap between all these disorders (Goes et al., 2016; Power et al., 2013). Although further work will be needed to examine the exact genetic determinants of SZ, we hypothesize that this association can aid in a more detailed understanding of SZ and related disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We examined the previously identified association of reduced gray matter concentration in the insula - medial prefrontal cortex and a quantitative trait locus located in 12q24 in a SZ dataset.
- A parallel independent component analysis (pICA) was used to examine the associations in 409 individuals with schizophrenia and 421 healthy controls.
- The insula – mPFC gray matter component was negatively correlated with a genetic component involved in the QTL.
- The protein-coding genes contributing to the correlated genetic component have been implicated in psychiatric disorders, immune response, and neuroinflammation.

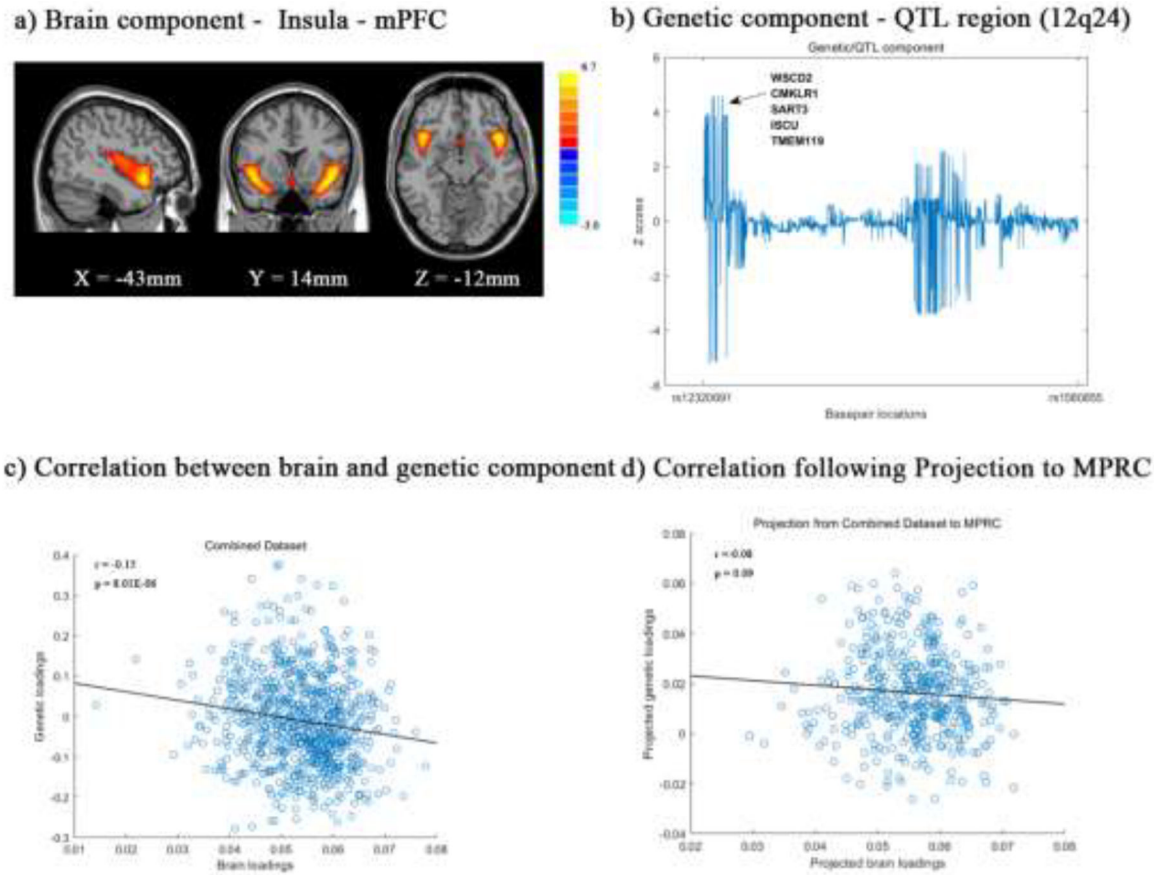

Figure 1.

The pICA and projection results of the structural brain and QTL components. a) The brain component includes mainly the insula and medial prefrontal cortex (MPFC). Warm colors indicate positive *z* scores, and cool colors indicate negative *z* scores (see color map); b) QTL/genetic component, and the highly contributed SNPs/genes (*z* score ≥ 3); c) The brain component loadings correlated with the genetic loadings; d) The correlation between brain component loadings and genetic loadings after being projection from the Combined dataset onto the MPRC dataset.

Table 1.

Highlighted SNPs/Genes in QTL region

Full Name Gene	Gene Symbol	SNPs	CHR:BP	Location	Peak Z Score	Potential Brain Disorder	Potential Functional Annotation/ Phenotypes
Chemerin Chemokine-Like Receptor 1	CMKLR1	rs4964242	12:108302860	Intronic	5.2	____	peptide ligand-binding
		rs12321936	12:108332769	Intronic			
WSC Domain Containing 2	WSCD2	rs12425325	12:108211794	Intronic	3.9	Bipolar disorder	extraversion
		rs10778617	12:108220126	Intronic/Coding			
		rs3764002	12:108224853	Coding			
		rs1346173	12:108241683	Intronic			
		rs75980172	12:108243124	Intronic			
Transmembrane Protein 119	TMEM119	rs73191228	12:108596806	Intronic	3.9	Alzheimer's disease	neuroinflammation
Iron-Sulfur Cluster Assembly Enzyme	ISCU	rs10492251	12:108571306	3 Downstream	3.9	____	metabolism, iron homeostasis, and oxidative stress response
Spliceosome Associated Factor 3, U4/U6 Recycling Protein	SART3	rs11113977	12:108528508	Intronic	3.8	____	tumor-rejection antigen
		rs4964721	12:108541762	Intronic/3 Downstream			
		rs4964264	12:108541781	Intronic/3 Downstream			
		rs888555	12:108542708	Intronic/3 Downstream			
		rs715447	12:108552942	Intronic/Non-Coding Intronic			
		rs1016881	12:108556190	Intronic/Non-Coding/5 Upstream			
		rs11837563	12:108562649	5 Upstream/ Non-Coding/ Coding			

Note: Only SNPs with Z value ≥ 3 were annotated. CHR: Chromosome; BP: Base Pair.