Archival Report

Biological Psychiatry

Connectome Disconnectivity and Cortical Gene Expression in Patients With Schizophrenia

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ABSTRACT

BACKGROUND: Genome-wide association studies have identified several common risk loci for schizophrenia (SCZ). In parallel, neuroimaging studies have shown consistent findings of widespread white matter disconnectivity in patients with SCZ.

METHODS: We examined the role of genes in brain connectivity in patients with SCZ by combining transcriptional profiles of 43 SCZ risk genes identified by the recent genome-wide association study of the Schizophrenia Working Group of the Psychiatric Genomics Consortium with data on macroscale connectivity reductions in patients with SCZ. Expression profiles of 43 Psychiatric Genomics Consortium SCZ risk genes were extracted from the Allen Human Brain Atlas, and their average profile across the cortex was correlated to the pattern of cortical disconnectivity as derived from diffusion-weighted magnetic resonance imaging data of patients with SCZ ($n = 48$) and matched healthy controls ($n = 43$).

RESULTS: The expression profile of SCZ risk genes across cortical regions was significantly correlated with the regional macroscale disconnectivity ($r = .588$; $p = .017$). In addition, effects were found to be potentially specific to SCZ, with transcriptional profiles not related to cortical disconnectivity in patients with bipolar I disorder (diffusion-weighted magnetic resonance imaging data; 216 patients, 144 controls). Further examination of correlations across all 20,737 genes present in the Allen Human Brain Atlas showed the set of top 100 strongest correlating genes to display significant enrichment for the disorder, potentially identifying new genes involved in the pathophysiology of SCZ.

CONCLUSIONS: Our results suggest that under disease conditions, cortical areas with pronounced expression of risk genes implicated in SCZ form central areas for white matter disconnectivity.

Keywords: Brain network, Connectivity, Connectomics, Diffusion MRI, Gene expression, Psychiatry, Schizophrenia

http://dx.doi.org/10.1016/j.biopsych.2016.07.012

Schizophrenia (SCZ) is a psychiatric disorder that is characterized by hallucinations, delusions, a loss of initiative, and cognitive dysfunction. The illness has an estimated heritability up to 85% (1,2), with the recent genome-wide association study (GWAS) of the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC) identifying at least 108 common associated loci (3). The disorder is also reported to include reductions in synapses (4,5), dysfunction of neurotransmitters (6), loss of gray matter volume (7), and alterations in brain connectivity architecture (8–13)—effects that together have been posited to lead to changes in neural communication efficacy and affected information integration (14,15). Notably, twin (16,17) and family studies (18,19) have shown the high heritability of global white matter disconnectivity, suggesting that risk genes play a role in mediating changes in white matter volume (20–22) and more specifically corticocortical pathways (23–25). The pathogenetic mechanisms of how these risk genes relate to alterations in connectome structure remain unknown.

Animal models represent a valuable tool for studying the underlying genetic mechanisms for brain phenotypes (26,27). For example, mouse models have shown that the expression of risk genes affects neural function and cognitive processing (26) and dysfunction of subcortical structures (27). An additional approach involves the examination of brain phenotypes in the context of transcriptional profiles (28–30). With genes known to have distinct expression across brain regions, an advantage of this method is the possibility to investigate region-specific expression patterns of disease-associated genes, which in turn can lead to insights in pathogenetic mechanisms of morphologic brain changes in disease conditions (31). Adopting this approach, we performed a cross-correlation study in which we combined comprehensive expression levels of SCZ risk genes extracted from the open database of the Allen Human Brain Atlas (AHBA) (32) with data from diffusion-weighted magnetic resonance imaging (MRI) in patients with SCZ. SCZ risk genes were selected as the set of single genes on risk loci identified by the Schizophrenia Working Group of the PGC, and their pattern of expression across cortical areas was cross-correlated with data on macroscale disconnectivity derived

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ISSN: 0006-3223

Biological Psychiatry March 15, 2017; 81:495–502 www.sobp.org/journal

from connectome MRI in patients with SCZ (9). Cross-correlation analysis showed default transcriptional profiles of SCZ risk genes across the cortex to be associated with cortical patterns of macroscale disconnectivity, indicating regions with pronounced expression of risk genes to bear the strongest reductions in corticocortical connectivity observed with SCZ.

METHODS AND MATERIALS

Cortical Gene Expression of SCZ Risk Genes

The AHBA (32) was used to extract transcriptional profiles across brain areas, including a unique database of expression levels of 20,737 genes represented by 58,692 probes across the complete cortical mantle as collected from postmortem brains of six human donors without a history of psychiatric or neuropathological disorders (summary of demographics shown in Supplemental Table S1). With data of all six donors available for the left hemisphere (two for the right hemisphere), samples of the left hemisphere were included for analysis. Cortical samples were volumetrically mapped to the Desikan–Killiany cortical parcellation atlas (DK; 57 regions per hemisphere) (Figure 1) (33), computing the minimal Euclidean distance of the reported Montreal Neurological Institute three-dimensional coordinates of each donor sample to the Montreal Neurological Institute coordinates of all voxels of FreeSurfer's software's fsaverage subject (available at http://surfer.nmr.mgh.harvard.edu/) (Supplemental Methods). A maximal distance threshold of 1 mm was applied (Supplemental Methods). Next, a gene expression profile was computed for each DK region by averaging the expression profiles of the donor samples mapped to that particular DK region. The recent GWAS study of the PGC reported that 43 of 108 SCZ risk loci were linked to a single gene (3). Default expression levels of those 43 single PGC genes (tabulated in Supplemental Table S2) were extracted from the total set of 20,737 genes (Supplemental Methods) and combined into a schizophrenia risk gene expression (SRGE) score by averaging the AHBA normalized expression levels across the selected 43 PGC genes, per cortical area (Figure 2A). Two post hoc analyses were performed in which additional SRGE profiles were examined by 1) including an additional set of 15 genes located within 500 kb of the 108 PGC loci, resulting in a total of 43 + 15 additional SCZ risk genes, and 2) including all genes (N = 349, including both single and multigene-associated loci) related to the 108 SCZ-associated loci. Data of these post hoc analyses are reported in the Supplemental Results.

A SRGE profile was also computed for the set of 85 genes as reported by the recent meta-analysis by Chen *et al.* (34) in which the top findings of GWAS were combined and summarized. While the Chen *et al.* dataset included only 13 single genes (limiting cross-correlation analysis), multigene associated loci were included in this validation analysis (Supplemental Table S2).

Diffusion-Weighted Imaging Macroscale Connectivity in Patients

3T MRI scans were acquired for a group of 48 patients with SCZ and 43 age- and sex-matched healthy control subjects (demographics shown in Supplemental Table S3), a dataset previously examined in the context of hub and rich club disconnectivity in SCZ (9). In short, for each participant, two diffusion-weighted imaging (DWI) sets of 30 diffusion-weighted volumes (b = 1000 s/mm^2) and five unweighted volumes were acquired. Compressed sensing techniques were applied to determine the diffusion profile for each voxel, allowing for the reconstruction of complex fiber architectures,

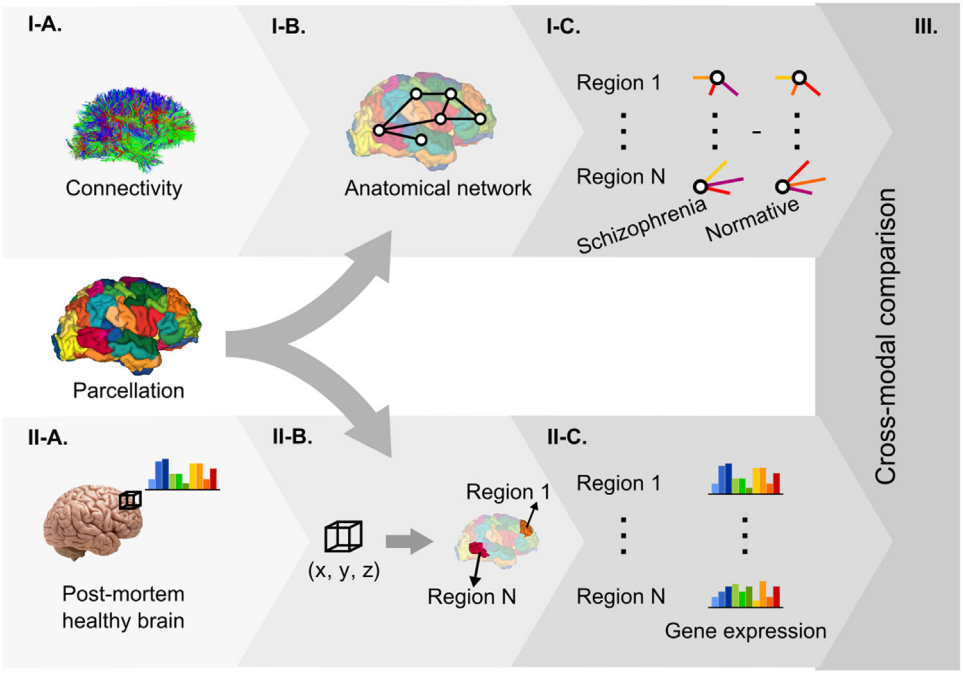

Figure 1. Overview of data processing and analysis. **(I-A)** Streamline tractography was used to reconstruct individual white matter corticocortical pathways. **(I-B)** Corticocortical connectivity was reconstructed between all 57 Desikan–Killiany (DK) regions and **(I-C)** the patient-control pattern of regional disconnectivity was computed. **(II-A)** Cortical gene expression of 20,737 genes was extracted from the Allen Human Brain Atlas (AHBA). **(II-B)** The reported AHBA samples were mapped to cortical areas of the DK atlas. **(II-C)** Gene expression levels of the 43 Psychiatric Genomics Consortium schizophrenia risk genes (3) were extracted, and for each DK-57 region a schizophrenia risk gene expression value was computed as the average of the AHBA-normalized (32) expression values of the 43 schizophrenia risk genes. **(III)** The obtained cortical schizophrenia risk gene expression profile was correlated to disease-related macroscale connectivity reductions derived from neuroimaging data.

with deterministic streamline tractography used to trace white matter pathways (9) (Supplemental Methods). High-resolution anatomical T1-weighted images were used for tissue classification, surface reconstruction, and subsequent division of the cortical mantle into 57 distinct areas according to the DK atlas (i.e., the atlas also used to map the AHBA data). A structural connectome map was formed for each individual dataset by determining, for each pair of cortical regions, whether they were connected by corticocortical streamlines from the total set of reconstructed fiber streamlines. Connection strength of the resulting corticocortical pathways was taken in terms of number of interconnecting streamlines (NOS) (14,35). We also included the examination of streamline density (SD), computed as the NOS between two regions dividing off the volume of the two connected regions (35,36), to correct for potential differences in regional and total brain volume as often reported in patients with SCZ. Fractional anisotropy (FA) and mean diffusivity (MD) of tracts were examined to obtain insight into potential changes in microstructural organization. Next, for each of the individual datasets, for each of the 57 DK cortical areas, we assessed the metric of regional connectivity [i.e., nodal strength in terms of graph theoretical connectome studies (37); see Supplemental Methods], computed as the total sum (i.e., nonzero mean in case of FA/MD) of connectivity per region. Subsequently, patient-control between-group differences in regional disconnectivity were computed as the ratio of change in cortical connectivity between the patient and control populations (i.e., [patients – controls]/[controls]) per cortical area (Figure 2B). The resulting cortical map reflected regional variation in macroscale disconnectivity in the group of patients compared to the group of controls. Expressing patient-control differences per cortical area in terms of *t* statistics reveals consistent findings (Supplemental Results). In addition, similar findings are also observed when using coarser (i.e., DK-34 instead of 57 regions per hemisphere) or finer (i.e., DK-111 regions per hemisphere) parcellation versions of the DK atlas and the Automatic Anatomical Labeling atlas (data shown in the Supplement).

Cross-Modal Gene Connectivity Analysis

Associations between transcriptional profiles of risk genes and patient-control differences in macroscale connectivity were assessed using Pearson's correlation analysis. Statistical evaluation was performed using permutation testing (e.g., selecting equally sized sets of random genes and examining their null effect correlation to cortical macroscale disconnectivity [10,000 permutations examined; see the Supplement]). In addition, because averaging gene expression across genes in distinct molecular pathways (as we did for the SRGE profile) can be nonoptimal given that signals of different sources are mixed, we alternatively computed individual correlations between all of the 43 single PGC genes and the pattern of cortical disconnectivity and then averaged their absolute correlation values. Similarly, permutation testing selecting equally sized sets of random genes and examining their average absolute null effect correlation was used for statistical evaluation. The false discovery rate (FDR) was used to correct for multiple testing (Supplement).

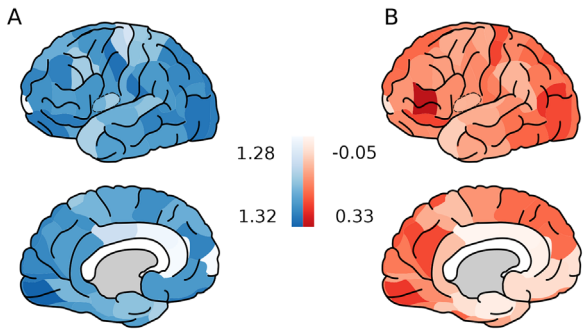

Figure 2. Side-to-side view of **(A)** cortical pattern of gene expression of schizophrenia risk genes and **(B)** cortical distribution of reductions in macroscale regional disconnectivity between patients and controls across the mapped Desikan–Killiany regions.

Gene Classes

Correlation analyses were performed for the six specific gene classes as specified by the Schizophrenia Working Group of the PGC (3). This PGC subdividion included the grouping of 35 genes (of the 349 PGC risk genes related to the 108 loci) into six subclasses, following current hypotheses on disease etiology and treatment. These groupings were related to the following: 1) therapeutic targets (2 genes); 2) glutamatergic neurotransmission (6 genes); 3) calcium signaling (7 genes); 4) synaptic function and plasticity (9 genes); 5) other neuronal ion channels (5 genes); and 6) neurodevelopment (7 genes). Average gene expression profiles were computed for each class and correlated to the cortical pattern of DWI macroscale disconnectivity.

Strongest Correlating Genes

Next, we cross-correlated the regional expression profile of each of the 20,737 AHBA genes individually with the pattern of MRI disconnectivity. The top 100 (and additionally top 200) strongest correlating genes (absolute correlations; all genes listed in Supplemental Table S3) were further examined by means of three post hoc analyses.

We first examined the role of the selected top 100 (and additionally top 200) strongest correlating genes using a PubMed and Google Scholar search, in which we searched for scientific publications that reported on the involvement of these genes in SCZ or other psychiatric disorders. For each of the strongest correlating genes, we searched for the combination of (gene symbol) AND [(schizophrenia) OR (other psychiatric disorder)] and listed the publications reporting abnormalities in disease. The category of "other psychiatric disorder" included bipolar disorder, autism, attention-deficit/hyperactivity disorder, major depressive disorder, obsessive-compulsive disorder, or alcohol addiction. We assessed statistical evaluation on the number of reports observed by means of computing the level of chance of randomly selecting 100 genes involved in SCZ out of the total number of 20,737 AHBA genes, with an estimated total number of 2800 genes involved in the disorder [based on (38); see Supplement for details].

Second, we examined the selected set of top 100 (and additionally top 200) correlating genes by cross-validating these genes with the recently published GWAS data of the PGC (3) (Supplement) extracting odds ratios and *p* values of the set of strongest correlating genes. In addition, we specifically examined

the subset of genes out of these top strongest correlating genes that did not reveal any hits in our PubMed/Google Scholar search (i.e., examining the set of genes that have not previously been mentioned in the context of SCZ or other psychiatric disorders).

Third, we performed gene pathway analysis for the top scoring genes using Protein ANalysis THrough Evolutionary Relationships (PANTHER) analysis (39) and the web interface of ConsensusPathDB tool (40). Reported p values were corrected for multiple comparisons using FDR.

RESULTS

Correlation analysis revealed a significant correlation between SRGE profile and the pattern of white matter disconnectivity (NOS: $r = .588$; $p = .017$ [Figure 3]; SD: $r = .548$, $p = .0277$ [Supplemental Figure S1]; permutation testing, both surviving FDR), indicating that cortical regions with the highest expression of risk genes overlap with areas that show the largest reduction in white matter connectome connectivity. This correlation was particularly observed for metrics reflecting reductions in regional connectivity in terms of white matter volume [i.e., NOS and SD (35)], with no correlation effects observed when examining MRI metrics of white matter microstructure (i.e., FA [$p = .982$] and MD [$p = .831$]). Alternatively, taking the average value across all individual correlations of the 43 PGC genes confirmed a positive relationship between the pattern of expression of risk genes and regional disconnectivity (average $r = .322$, $p = .0005$, permutation testing [Supplemental Figure S2]). Analysis of the set of 43 + 15 genes within 500 kb and the subset of 349 genes within all 108 PGC-identified loci revealed similar findings (Supplemental Results).

No correlation was observed between SRGE and disease-related pattern of cortical thinning (computed as the ratio of change in cortical thickness between patients and controls, $r = .2803$, $p = .1422$, permutation testing [Supplement]), suggesting an effect specific to patterns of regional connectome disconnectivity.

Similar associations were also observed with gene expression levels based on 85 SCZ risk genes reported in the Chen *et al.* study (34) (NOS: $r = .600$, $p = .0071$; SD: $r = .585$, $p = .0058$; permutation testing [Supplemental Figure S3]).

PGC Gene Classes

We examined the subset of 35 risk genes specifically highlighted and grouped by the PGC into six functional gene classes following current hypotheses on SCZ etiology and treatment (3). Correlation analysis between pattern of disconnectivity and pattern of gene expression showed the strongest association for the class of genes involved in neuronal calcium signaling (Table 1), suggesting a potentially strong influence of this class of genes on reductions in macroscale connectivity in patients (NOS: $r = .680$, $p = .0008$ [Figure 4]; SD: $r = .632$, $p = .0018$; all surviving FDR [Supplemental Figure S4]). Given this strong correlation, we further examined to what extent our main effect (i.e., SRGE based on 43 single PGC genes) was driven by the subclass of neuronal calcium signaling genes. Excluding the subclass of neuronal calcium signaling genes from the set of single genes (i.e., 43 minus the 5 of 7 calcium signaling genes) (Supplemental Methods) still revealed a significant correlation between the expression profile of the remaining set of 38 genes and regional disconnectivity ($r = .576$, $p = .024$; permutation testing).

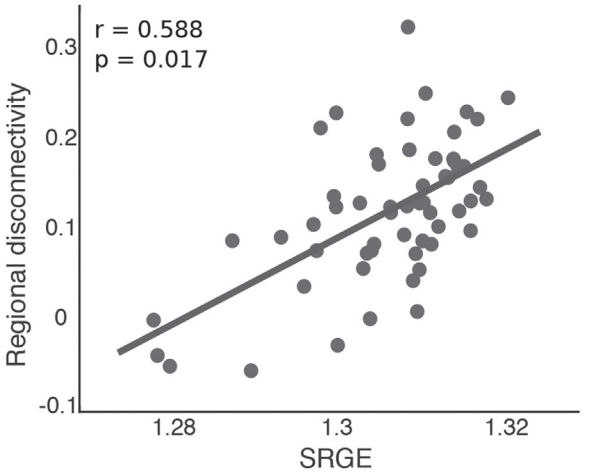

Figure 3. Positive association between default schizophrenia risk gene expression (SRGE, x-axis) and between-group differences in macroscale regional disconnectivity (number of streamlines, y-axis). A similar positive correlation was observed for streamline density effects (Supplemental Figure S1).

Top Strongest Correlating Genes

We continued by examining the correlation for each of the 20,737 AHBA genes individually and selecting the top 100 (and additionally top 200) strongest correlating genes. First, a PubMed/Google Scholar search on the set of top 100 (all $p < 1.56 \times 10^{-6}$, all individually surviving strict Bonferroni correction) genes revealed 34 genes to be previously reported in context of SCZ in at least one scientific study, which is 2.2 times more than one would expect under the null condition ($p = 1.35 \times 10^{-5}$ [Supplemental Table S3 lists all of the found studies]). In addition, of the remaining 66 genes, another 17 genes were previously reported in the context of other psychiatric disorders, including bipolar disorder (5 genes), autism spectrum disorder (4 genes), obsessive-compulsive disorder (3 genes), attention-deficit/hyperactivity disorder (3 genes), and alcohol addiction (1 gene) (Supplemental Table S4). Examining the top 200 strongest correlating genes (again, all individually surviving Bonferroni correction) revealed similar findings: 96 genes were found to be previously reported in the context of psychiatric conditions, with 71 genes reported in SCZ ($p < .0001$) and 25 genes reported in context of other psychiatric conditions (Supplemental Results).

Second, we cross-referenced the subset of top 100 strongest correlating genes with the recently published GWAS data of the PGC (3), which revealed a trend toward higher involvement of this subset of genes in the disorder with an average odds ratio deviating from 1 of 0.0372 ($p = .0172$; permutation testing). In addition, specifically examining the subset of 49 genes not earlier reported in context of psychiatric disorders also revealed a trend toward higher involvement (average PGC odds ratios deviating from 1 of 0.0327, $p = .110$; permutation testing), indicating the potential involvement of "new genes" in the pathophysiology of SCZ. Similar effects were observed

Table 1. Correlation Analyses Gene Classes

Functional Class	No. of Genes	Correlation Coefficient	*p* Value[a]
Neuronal Calcium Signaling	7	0.680	.0008
Glutamatergic Neurotransmission	6	–0.112	.7520
Neurodevelopment	7	0.337	.3080
Synaptic Function and Plasticity	9	0.225	.5244
Other Neuronal Ion Channels	5	0.314	.3531
Therapeutic Targets	2	–0.383	.2152

[a]*p* values assessed with permutation testing (10,000 permutations).

when we examined GWAS *p* values and odds ratios of the top 200 strongest correlating genes (Supplemental Results). This was again true for the remaining subset of the not previously reported 104 genes out of the top 200 strongest correlating genes (average PGC odds ratio deviating from 1 of 0.0346, $p = .048$; permutation testing) (Supplement), suggesting potential enrichment of the set of top strongest correlating genes in SCZ.

Third, PANTHER overrepresentation analysis (39) revealed strong overrepresentation of the top 100 strongest correlating genes in the biological processes of synaptic transmission ($p = 1.80 \times 10^{-8}$), cell–cell signaling ($p = 2.80 \times 10^{-7}$), and regulation of cell and protein localization ($p = 8.06 \times 10^{-6}$; all surviving FDR). Additional analysis by means of the web interface of the ConsensusPathDB tool (40) showed significant overrepresentation of 54 gene ontology terms (tabulated in Supplemental Table S4), centralized around processes involved in cell–cell signaling and secretion ($p < 1.15 \times 10^{-3}$), protein complex formation ($p < 5.0 \times 10^{-3}$), and regulation of synapse structure or activity ($p < 2.60 \times 10^{-3}$; all FDR)—processes that have all been reported to be involved in the pathophysiology of SCZ (41–43). Examining the top 200 genes confirmed these findings, with PANTHER analysis highlighting overrepresentation of biological processes involved in synaptic transmission ($p < 1.31 \times 10^{-5}$) and regulation of (ion) transmembrane transport ($p < 6.69 \times 10^{-3}$; all surviving FDR). ConsensusPathDB analysis revealed gene pathways related to formation and regulation of synapses and cell–cell signaling ($p < 1.00 \times 10^{-3}$) and structure and activity of transporters and receptors ($p < 7.58 \times 10^{-3}$; all FDR) (Supplemental Table S5).

A total set of 540 genes all individually survived strict Bonferroni correction (i.e., showing a $p < .05$ corrected for 20,737 tests). A PGC GWAS cross-validation and overrepresentation analysis for this set of 540 top-scoring genes revealed similar pathways, including (regulation of) potassium ion transmembrane transport, single organism signaling, and cell communication (see Supplement for an overview).

Bipolar Disorder Validation

Analysis of the expression profile of SCZ risk genes (SRGE) and MRI connectivity reductions in the patients with bipolar disorder did not reveal associations in terms of DWI NOS ($p = .506$), SD ($p = .400$), FA ($p = .302$), or MD ($p = .078$) (Supplemental Results). Similarly, in further support of a certain level of specificity of the reported effects to SCZ, correlation analysis between bipolar risk gene expression levels and the pattern of SCZ disconnectivity also did not reveal significant relationships in NOS, SD, nor FA/MD

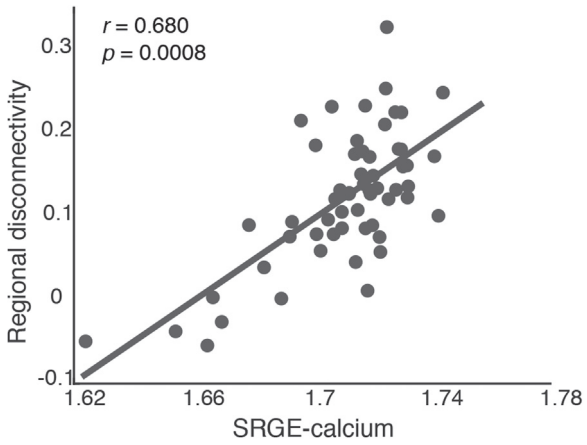

Figure 4. Positive association between default gene expression levels of the class of Psychiatric Genomics Consortium risk genes related to neuronal calcium signaling (x-axis) and the pattern of macroscale disconnectivity (number of streamlines, y-axis). A similar positive correlation was observed for streamline density effects (Supplemental Figure S3). SRGE, schizophrenia risk gene expression.

(Supplemental Results). In contrast, linking bipolar risk gene expression levels to the MRI measurements of connectivity in the bipolar group revealed a significant inverse association between bipolar risk gene expression levels and regional disconnectivity in patients with bipolar disorder, in particular as measured by means of changes in FA of corticocortical tracts (set I: FA: $r = –.530$, $p = .0007$; set II: FA: $r = –.392$, $p = .0025$; surviving FDR) (see Supplemental Figure S5 and Supplemental Results for other connectivity metrics).

DISCUSSION

Our findings report the cortical transcriptional profile of SCZ risk genes to be associated with the phenotype of regional white matter connectome disconnectivity in patients with SCZ. This suggests that under disease conditions, cortical areas with pronounced expression of risk genes might be central areas for global white matter disconnectivity.

Our observations support and extend findings of studies using genetic material from blood samples linking genetic information to changes in brain morphology. The Enhancing NeuroImaging Genetics through Meta-Analysis consortium, for example, showed strong heritability of subcortical volume loss in SCZ (44), and the deletion burden of SCZ-associated copy number variations has been shown to be associated with changes in anatomical and functional connectivity in patients with SCZ (45).

Examining PGC gene subclasses showed a particularly strong (but not exclusive) association between the pattern of regional disconnectivity and the average expression profile of genes related to neuronal calcium signaling. Calcium signaling has indeed been noted to be of particular importance in the etiology of SCZ (46–48), with proteins such as RGS4, GAP43, and parvalbumin regularly reported to have a role in the disorder (47). In addition, a risk variant of calcium gene *CACNA1C*—a gene repeatedly associated with SCZ—is involved in the

regulation of cellular calcium influx and has been directly linked to white matter integrity loss in SCZ (49). Moreover, at the cellular level, calcium signaling has been noted to play a central role in the formation, degeneration, and modification of neuronal connectivity (50,51) with up- and down-regulation of calcium signaling leading to reductions in dendritic volume and branching (50,52). SCZ indeed involves pronounced reductions in spine density of layer 3 pyramidal cells in frontal and temporal association regions (5), with these changes argued to be related to the extent of macroscale white matter disconnectivity (53).

Pathway analysis of the top 100 (and additionally top 200) strongest correlating genes revealed a particular role for pathways involved in the formation of synapses and protein complexes (41,42,54). A literature search on these top-correlating genes suggested a substantial part (51/100) to be previously reported in the context of psychiatric disorders, which makes us believe that additional examination of the remaining set of genes may a fruitful approach to identify new risk genes (55). This is strengthened by two of our observations: first, cross-referencing the set of remaining genes not earlier reported in context of pyschiatric disorder with GWAS data of the PGC (3) reveals potential enrichment of this subset of genes in the disorder, showing higher odds ratios deviating from 1 and overall low GWAS *p* values. Second, several of the top-scoring genes have been earlier reported in context of the disorder. We stress, for example, the recently discovered gene *C4A* within the major histocompatibility complex on chromosome 6 (56), which scored particularly high out of all possible correlations, namely position 15 out of all 20,737 genes ($r = -.6978$, $p = 1.6215 \times 10^{-9}$; surviving FDR and strict Bonferroni) (Supplement).

Moreover, of all 11,307 genes showing an inverse relationship with the cortical pattern of macroscale disconnectivity, *C4A* turned out to be the second strongest correlating gene, with only *ZFP36L1* showing a stronger inverse association ($r = -.7102$, $p = 6.1183 \times 10^{-10}$)—again, a gene that was earlier noted to be involved in the disorder (57). As suggested for *C4A* (56), *ZFP36L1* (58) is a gene related to regularization processes. Underlying pathogenetic mechanisms of both observed positively versus inversely correlated effects remain elusive for now. A potential explanation might include a distinction between genes having a regulatory role (e.g., *C4A* and *ZFP36L1*) compared with genes related to biological processes, such as the subset of genes involved in calcium signaling.

Our findings also show potential specificity of the observed effects to SCZ. Cortical expression profiles of SCZ risk genes did not show correlations to the pattern of regional white matter disconnectivity in patients with bipolar I disorder, nor did we observe effects of bipolar risk genes on macroscale disconnectivity in the group of patients with SCZ. In contrast, in favor of potential disorder-specific associations, the expression profile of bipolar risk genes did show a significant correlation with the cortical pattern of FA-related disconnectivity in patients with bipolar disorder (59). These findings argue for potentially converging pathophysiologic mechanisms in the two disorders (60). Indeed, the diffusion-weighted MRI metric of FA is often interpreted as a proxy of white matter microstructure—rather than a metric of tract volume (35)—and studies have suggested white matter abnormalities in bipolar disorder to be concentrated around a reduction in myelin content rather than abnormalities in axonal geometry or tract volume (61,62). This is in contrast to SCZ, where both myelination deficits and axon abnormalities have been reported (63).

Several remarks have to be made when interpreting the findings of our cross-correlation study. The transcriptional profiles obtained from the AHBA include data from non-psychiatric postmortem donors, which was cross-correlated to cortical patterns of disconnectivity as derived from MRI scans of a group of patients with SCZ and healthy controls. This study design is therefore limited to examining relationships between cortical patterns of gene expression and regional macroscale disconnectivity across groups, with an examination of possible individual patient effects thus out of scope. However, the start of large-scale psychiatric brain banks (e.g., the National Institute of Mental Health Brain Collection (64) and the Netherlands Brain Bank Psychiatry, http://www.nbb-psy.nl) may make the examination of a direct link between postmortem-measured connectivity changes and affected gene expression levels in individual patients possible in the near future. We also note that DWI is a technique that relies on water diffusion as an indirect marker for axon geometry, which is currently the only technique suitable to assess anatomical connectivity changes in patient populations in vivo. Diffusion MRI is generally recognized to have limitations with respect to the reconstruction of complex fiber architectures and connectome mappings (35,65,66), effects that may have potentially led to an underestimation of the observed patient MRI effects.

Our findings suggest expression profiles of SCZ risk genes across brain areas to coincide with patterns of white matter disconnectivity in patients with SCZ, elucidating possible genetic underpinnings of white matter connectivity disruptions in the disorder. Linking expression levels to disease phenotypes can form a valuable tool to provide insight into the pathogenetic mechanisms of SCZ. Importantly, the applied cross-modal analysis may include a potential powerful approach for identifying new risk genes and gene pathways involved in SCZ.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by a Vidi Grant of the Dutch Research Council (Netherlands Organisation for Scientific Research Grant No. VIDI-452-16-015 to MPvdH) and a MQ Fellowship (to MPvdH). Funding agencies did not have any influence on the data acquisition, analysis, or reporting of the data.

We thank Guusje Collin for helping with the bipolar imaging data and for fruitful discussions.

All authors report no biomedical financial interests or potential conflicts of interest.

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Received Apr 1, 2016; revised July 16, 2016; accepted July 18, 2016.

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.biopsych.2016.07.012.

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