Association of Genetic Variants on 15q12 With Cortical Thickness and Cognition in Schizophrenia

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Context: Cortical thickness is a highly heritable structural brain measurement, and reduced thickness has been associated with schizophrenia, bipolar disorder, and decreased cognitive performance among healthy control individuals. Identifying genes that contribute to variation in cortical thickness provides a means to elucidate some of the biological mechanisms underlying these diseases and general cognitive abilities.

Objectives: To identify common genetic variants that affect cortical thickness in patients with schizophrenia, patients with bipolar disorder, and controls and to test these variants for association with cognitive performance.

Design: A total of 597,198 single-nucleotide polymorphisms were tested for association with average cortical thickness in a genome-wide association study. Significantly associated single-nucleotide polymorphisms were tested for their effect on several measures of cognitive performance.

Setting: Four major hospitals in Oslo, Norway.

Participants: A total of 1054 case individuals and controls were analyzed in the genome-wide association study and follow-up cognitive study. The genome-wide association study included controls (n=181) and individuals with DSM-IV–diagnosed schizophrenia spectrum disorder (n=94), bipolar spectrum disorder (n=97), and other psychotic and affective disorders (n=49).

Main Outcome Measures: Cortical thickness measured with magnetic resonance imaging and cognitive performance as assessed by several neuropsychological tests.

Results: Two closely linked genetic variants (rs4906844 and rs11633924) within the Prader-Willi and Angelman syndrome region on chromosome 15q12 showed a genome-wide significant association (P=1.1×10−8) with average cortical thickness and modest association with cognitive performance (permuted P=0.03) specifically among patients diagnosed as having schizophrenia.

Conclusion: This genome-wide association study identifies a common genetic variant that contributes to the heritable reduction of cortical thickness in schizophrenia. These results highlight the usefulness of cortical thickness as an intermediate phenotype for neuropsychiatric diseases. Future independent replication studies are required to confirm these findings.

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CHZIOPHRENIA IS RECOGNIZED as one of the leading causes of morbidity around the world, with a lifetime risk of approximately 1% worldwide,\(^1\) and ranks as one of the most costly disorders affecting humans.\(^2\) The heritability of schizophrenia is high, estimated in most studies to be approximately 80%.\(^3,4\) Despite this, the mechanisms underlying susceptibility to schizophrenia remain elusive, likely due to the genetic and phenotypic heterogeneity of the disorder. The analysis of endophenotypes or “intermediate” phenotypes has great potential to reveal the genetic mechanisms underlying schizophrenia and other potentially related neuropsychiatric disorders, such as bipolar disorder. The power of this analytic strategy is derived from the observation that endophenotypes may reflect underlying pathologies associated with disease more proximal to genetic lesions. Also, it may help create more homogenous subtypes of schizophrenia that are amenable to genetic analysis.\(^6,7\) Therefore, we pursued a genome-wide association study (GWAS) leveraging variation in an endophenotype derived from structural brain measures that is thought to reflect a component of pathogenetic processes leading to, or associated with, schizophrenia.

Genetic association analyses focusing on the role of common DNA sequence variation and schizophrenia diagnosis without leveraging endophenotypes or an attempt to accommodate the likely heterogeneity associated with schizophrenia have been highly problematic. Indeed, only recently, GWASs have identified common single-nucleotide polymorphisms (SNPs) that

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show a reproducible association with the disease, but these SNPs have only moderate risk and odds ratios (ie, approximately 1.1-1.5).5,9 In contrast, the use of endophenotypes has resulted in some successes. For example, candidate gene studies have identified SNP associations with anatomical10-12 and functional13 brain measures, many of which can be considered intermediate phenotypes for schizophrenia. In addition, a recent GWAS identified SNPs associated with brain activation in schizophrenia.14 Although these candidate gene associations require further replication, they support the claim that common genetic variation can be associated with neural intermediate phenotypes of relevance to schizophrenia. Therefore, we undertook a GWAS approach to identify genes related to a specific structural brain measurement, cortical thickness, thought to play a role in mediating schizophrenia15-19 and potentially related disorders.

Previously, some of us20 have reported similarities and differences in cortical and subcortical brain structures between schizophrenia and bipolar disorder. The similarities between the disorders regarding neural phenotypes call into question strict diagnostic differences between them. In fact, traditional definitions of schizophrenia and bipolar disorder are being reevaluated by the psychiatric and research communities,21 and evidence is increasing that supports overlapping pathogenetic mechanisms and genetic susceptibility for these 2 disorders.22-26 Schizophrenia and bipolar disorder may, therefore, be perceived as dimensionally different or different in the degrees to which specific substrates or neural mechanisms are perturbed rather than as categorically separate disease entities.27 Our study, which includes individuals with schizophrenia and bipolar disorder, aims to identify neuronal and molecular mechanisms specific for schizophrenia and thus helps highlight distinct features of this disorder.

We focus specifically on cortical thickness as an appropriate endophenotype because this brain measure is highly heritable28 and also because widespread cortical thinning is consistently seen in first-episode and chronic schizophrenia.15-20 In addition, cortical thickness reduction is associated with lower cognitive performance in healthy and diseased populations, including decreases on several neuropsychological tests of executive function that have been observed among individuals with neuropsychiatric conditions.27,29,30 Therefore, our GWAS was pursued not only to identify common SNPs that are associated with variation in cortical thickness in schizophrenia but also to contrast these SNP effects among individuals with bipolar disorder and among the individuals independent of diagnosis. We also tested associated SNPs with cognitive performance among the patient groups.

### METHODS

#### STUDY PARTICIPANTS

A total of 1054 participants from the Thematically Organized Psychoses (TOP) study were analyzed, including 481 control individuals, 345 patients diagnosed as having schizophrenia spectrum disorder (SSD), 179 diagnosed as having bipolar spectrum disorder (BSD), 13 diagnosed as having major depressive disorder, and 36 diagnosed as having a psychotic disorder not otherwise specified. The SSD diagnoses included schizophrenia, schizoaffective, and schizoaffective disorders, and the BSD diagnoses included bipolar I, bipolar II, and bipolar disorder not otherwise specified.

The participants with clinically diagnosed conditions were recruited continuously from psychiatric units in 4 major hospitals in Oslo, Norway. Trained psychiatrists and clinical psychologists performed clinical assessments. Diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) Axis I disorders.31 The healthy control sample was randomly selected from the same catchment area and screened with an interview regarding severe mental illness and the Primary Care Evaluation of Mental Disorders.32

All analyses in this study included subsets of the 1043 participants from the TOP study. Some participants were included in all analyses but others were included in only 1 analysis, depending on the imaging, genotype, and cognitive data available for each participant. A total of 421 study participants (181 controls, 94 patients with SSD, 97 with BSD, and 49 with major depressive disorder or psychotic disorder not otherwise specified) had genotype data and magnetic resonance images available. These 421 individuals were included in the GWAS, with mean cortical thickness as the phenotype of interest.

A total of 754 study participants (368 controls, 208 patients with SSD, and 178 patients with BSD), including 371 individuals from the initial GWAS, had cognitive and appropriate genotype data and were included in the follow-up association analyses involving cognitive performance as the phenotype of interest. A total of 826 study participants (ie, 481 controls and 345 patients with SSD) had cognitive measurements (but not necessarily genotype data) and were used to estimate the effect of schizophrenia diagnosis on cognition (Table 1 and eTable 1; http://www.archgenpsychiatry.com; for details, see Rimol et al15 and Simonsen et al31). Schizophrenia symptom severity, as assessed by the Positive and Negative Syndrome Scale, was comparable in the 3 groups of patients with schizophrenia studied in the GWAS (mean [SD] total score, 60.8 [13.4]), cognitive and genotype association (61.9 [15.0]), and cognitive analysis (63.2 [16.2]). Individuals in each diagnostic group across analyses included approximately equal numbers of men and women, were similar ages (range, 18-65 years), and had comparable IQs (see Table 2 for details).

### GENOTYPING

DNA was extracted from blood and genotyped on the Affymetrix 6.0 array, as previously reported.36,37 All TOP participants self-reported Norwegian ancestry. A total of 597 198 SNPs passed quality control filters (call rate >95%, minor allele frequency >5%, Hardy-Weinberg disequilibrium $P < 1 \times 10^{-6}$) and were merged with HapMap 3 reference populations. Principal component analysis of an allele-sharing distance matrix across all study participants did not suggest any genetic outliers.

### IMPUTATION

The TOP study genotypes were merged with the HapMap CEU reference population, which also included genetic variant information from the sequencing by the 1000 Genomes Project. To impute genotypes, MACH was used with the default settings, and only SNPs that passed imputation quality control (R > 0.5) were included for further analysis.

### IMAGING

Magnetic resonance imaging was performed with a 1.5-T Siemens Magnetom Sonata scanner (Siemens Medical Solutions...
USA Inc, Malvern, Pennsylvania) equipped with a standard head coil. Acquisition parameters were optimized for increased gray and white matter image contrast. Brain images were segmented with the FreeSurfer software package (http://freesurfer-software.org). For more details, see the article by Rimol et al.20

NEUROCOGNITIVE ASSESSMENT

Psychologists trained in standardized neuropsychological testing performed neurocognitive assessment. A 3-hour battery (including measures of estimated premorbid IQ and adequate test effort) was administered in a fixed order with 2 breaks with refreshments. For this analysis, we focused on 17 measures from 3 tests that made various demands on executive function and other cognitive domains. Among those measures were the letter fluency, category fluency, category switching, and repetition and set-loss error components from the Delis-Kaplan Executive Function System (D-KEFS)34 Verbal Fluency Test. Additional measures were the repetitions and intrusions, long delay free recall, and semantic, subjective, and serial clustering components of the California Verbal Learning Test (CVLT-II)33 and the block design, matrix reasoning, and similarities components of the Weschler Abbreviated Scale of Intelligence (WASI) (Table 1 and eTable 2).35

STATISTICAL ANALYSIS

In each diagnostic group, we computed the mean, standard deviation, skew, and kurtosis of average cortical thickness measurements. We then tested whether these measurements deviated significantly from a gaussian distribution with a D’Agostino-Pearson omnibus K2 and a Shapiro-Wilk test of normality (eTable 2).

Table 1. Cognitive Test Performance in Patients With Schizophrenia by rs4906844 Genotype

<table>
<thead>
<tr>
<th>Test</th>
<th>SNP/SSD</th>
<th>SNP</th>
<th>SSD</th>
<th>SNP/SSD</th>
<th>SNP</th>
<th>SSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>List A total correct</td>
<td>-0.11</td>
<td>-10.8</td>
<td>1</td>
<td>.93</td>
<td>1.1 × 10−18</td>
<td></td>
</tr>
<tr>
<td>Long delay free recall</td>
<td>-0.02</td>
<td>-1.0</td>
<td>2</td>
<td>.89</td>
<td>6.5 × 10−14</td>
<td></td>
</tr>
<tr>
<td>List A trial 1</td>
<td>-0.08</td>
<td>-1.4</td>
<td>6</td>
<td>.67</td>
<td>1.2 × 10−16</td>
<td></td>
</tr>
<tr>
<td>Semantic clustering</td>
<td>-0.16</td>
<td>-1.1</td>
<td>14</td>
<td>.38</td>
<td>2.6 × 10−11</td>
<td></td>
</tr>
<tr>
<td>Subjective clustering</td>
<td>0.12</td>
<td>-0.5</td>
<td>-24</td>
<td>.17</td>
<td>2.1 × 10−16</td>
<td></td>
</tr>
<tr>
<td>Repetition</td>
<td>-0.49</td>
<td>0.9</td>
<td>-52</td>
<td>.24</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Serial clustering</td>
<td>0.17</td>
<td>0.1</td>
<td>NA</td>
<td>.07</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Intrusion</td>
<td>-0.26</td>
<td>0.3</td>
<td>NA</td>
<td>.59</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>D-KEFS Verbal Fluency Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category fluency</td>
<td>-0.60</td>
<td>-4.9</td>
<td>12</td>
<td>.12</td>
<td>1.5 × 10−16</td>
<td></td>
</tr>
<tr>
<td>Category switching: correct responses</td>
<td>-0.02</td>
<td>-3.8</td>
<td>1</td>
<td>.94</td>
<td>2.5 × 10−16</td>
<td></td>
</tr>
<tr>
<td>Category switching: switching accuracy</td>
<td>-0.08</td>
<td>-3.2</td>
<td>3</td>
<td>.77</td>
<td>7.8 × 10−16</td>
<td></td>
</tr>
<tr>
<td>Letter fluency</td>
<td>0.18</td>
<td>-3.3</td>
<td>-5</td>
<td>.64</td>
<td>3.5 × 10−16</td>
<td></td>
</tr>
<tr>
<td>Total repetition errors</td>
<td>-0.47</td>
<td>-0.5</td>
<td>97</td>
<td>.03</td>
<td>.003</td>
<td></td>
</tr>
<tr>
<td>Total set-loss errors</td>
<td>-0.36</td>
<td>0.2</td>
<td>NA</td>
<td>.08</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>WASI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block design</td>
<td>-1.09</td>
<td>-8.7</td>
<td>13</td>
<td>.25</td>
<td>2.6 × 10−36</td>
<td></td>
</tr>
<tr>
<td>Matrix reasoning</td>
<td>-0.53</td>
<td>-7.7</td>
<td>7</td>
<td>.59</td>
<td>5.3 × 10−36</td>
<td></td>
</tr>
<tr>
<td>Similarities</td>
<td>-0.73</td>
<td>-7.5</td>
<td>10</td>
<td>.45</td>
<td>4.0 × 10−10</td>
<td></td>
</tr>
<tr>
<td>Combined, MANOVA</td>
<td>0.15c</td>
<td>0.42c</td>
<td>NA</td>
<td>.03</td>
<td>3.5 × 10−09</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CVLT-II, California Verbal Learning Test; D-KEFS, Delis-Kaplan Executive Function System; MANOVA, multivariate analysis of variance; NA, not applicable; SNP, single-nucleotide polymorphism; SSD, schizophrenia spectrum disorder; WASI, Weschler Abbreviated Scale of Intelligence.

Effect size proportion was calculated for tests that were significantly associated with schizophrenia diagnosis. The SNP effect size represents the change in score per additional copy of the minor allele.

Table 2. Characteristics of Study Participants Included in the Genome-wide Association Study and Follow-up Analyses

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Diagnostic Group</th>
<th>No. of Participants</th>
<th>Male Sex Proportion</th>
<th>Age, Mean (SD), y</th>
<th>IQ, Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging, genotype</td>
<td>SSD</td>
<td>94</td>
<td>0.54</td>
<td>34.2 (9.0)</td>
<td>106.7 (13.2)</td>
</tr>
<tr>
<td>BSD</td>
<td>97</td>
<td>0.45</td>
<td>35.7 (11.1)</td>
<td>108.7 (11.3)</td>
<td></td>
</tr>
<tr>
<td>MDD or PDNOS</td>
<td>49</td>
<td>0.55</td>
<td>29.1 (8.8)</td>
<td>108.9 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>181</td>
<td>0.52</td>
<td>35.9 (9.5)</td>
<td>114.7 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Cognitive, genotype</td>
<td>SSD</td>
<td>208</td>
<td>0.53</td>
<td>33.1 (9.6)</td>
<td>103.4 (14.9)</td>
</tr>
<tr>
<td>BSD</td>
<td>178</td>
<td>0.42</td>
<td>36.9 (12.0)</td>
<td>108.2 (12.0)</td>
<td></td>
</tr>
<tr>
<td>MDD or PDNOS</td>
<td>368</td>
<td>0.51</td>
<td>34.7 (9.9)</td>
<td>113.5 (9.7)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>345</td>
<td>0.58</td>
<td>31.4 (9.5)</td>
<td>99.1 (16.2)</td>
<td></td>
</tr>
<tr>
<td>Cognitive</td>
<td>SSD</td>
<td>481</td>
<td>0.49</td>
<td>34.9 (10.2)</td>
<td>113.1 (10.0)</td>
</tr>
</tbody>
</table>

Abbreviations: BSD, bipolar spectrum disorder; MDD, major depressive disorder; PDNOS, psychotic disorder not otherwise specified; SSD, schizophrenia spectrum disorder.

Weschler Abbreviated Scale of Intelligence full-scale IQ was measured for 419 of 421 participants with magnetic resonance imaging and single-nucleotide polymorphism data.
3). For each SNP tested for association, we used PLINK to fit an additive linear model with minor allele count, sex, and age (and diagnosis in the combined study participant analysis) as predictors of average cortical thickness. For the most significantly associated SNP in schizophrenia, we fit a linear model with minor allele count, sex, and age as predictors of cortical thickness for each brain vertex across the cortical surface and generated a cortical map based on SNP −log10 (P values). Also, we divided patients with schizophrenia into 3 groups based on rs4906844 genotype, combined each group with controls, and fit a linear model with diagnosis, sex, and age as predictors of cortical thickness across the cortical surface. We generated a cortical map based on diagnosis −log10 (P values) for each genotype group.

Multivariate analysis of variance (MANOVA) was run with the R statistical software package to test the association of the SNP most strongly associated with cortical thickness, rs4906844, with cognitive phenotypes among patients with schizophrenia, while controlling for age and sex. A conservative Bonferroni-corrected P value threshold (dashed line) for genome-wide significance was set to P=1.67×10^-8. Two genotyped SNPs (rs4906844 and rs11633924) and several imputed SNPs surpassed this threshold and were genome-wide significant.

RESULTS

We tested each SNP in the GWAS with average cortical thickness in each of 3 study groups: SSD (n=94), BSD (n=97), and all participants in our study (n=421), including healthy controls (n=181), patients with SSD (studied in group 1) and BSD (studied in group 2), and patients with other psychotic and affective disorders (n=49). Cortical thickness measurements in each diagnostic group could not be distinguished from a gaussian distribution based on 2 tests of normality (eTable 3) and, therefore, were not transformed for the GWAS. We controlled for the effects of age and sex and set a conservative Bonferroni-corrected threshold for genome-wide significance (P=5×10^-8/3=1.67×10^-8) to accommodate our analyses involving 3 different subsets of study participants, as previously noted.

In the schizophrenia group, 2 SNPs (rs4906844 and rs11633924) were significantly associated (P=1.08×10^-8,
The rs4906844 genotype is associated with global cortical thinning that is more prominent in the frontotemporal regions. Brain maps show $-\log_{10}(P$ values) for the additive effect of the number of minor alleles on cortical thickness at each vertex, while controlling for age and sex.

The rs4906844 genotype is associated with a widespread reduction in cortical thickness (Figure 1, eFigure 1, and eFigure 2), but in the second and third groups, no SNP associations were significant genome-wide (eFigure 3 and eFigure 4). Because these 2 SNPs are perfectly correlated in our sample of patients with schizophrenia ($r^2=1.0$), we arbitrarily focused the rest of our analysis on 1 SNP (rs4906844). This analysis is consistent with results for closely linked SNPs, including rs11633924. The fact that 2 SNPs on the genotyping chip exhibited association and were in strong linkage disequilibrium confirms that our association was not likely to result from a genotyping artifact. We found that patients with schizophrenia who had 0 copies of the minor allele of SNP rs4906844 (genotype GG, $n=26$) have a mean (SD) cortical thickness of 2.27 (0.09) mm, patients with 1 copy (AG, $n=45$) have a mean (SD) thickness of 2.20 (0.09) mm, and patients with 2 copies of the minor allele (AA, $n=23$) have a mean (SD) thickness of 2.13 (0.09) mm. These results represent a 3% reduction in cortical thickness per copy of the minor allele and a strikingly large effect size based on the comparison of patients with schizophrenia who are homozygous for the major and minor alleles (Cohen $d = (2.27-2.13)/0.09 = 1.56$). The 3 genotypic groups of patients with schizophrenia did not significantly differ in age ($P=.72$), full-scale IQ ($P=.59$), or symptom severity ($P=.93$) as assessed by the Positive and Negative Syndrome Scale based on 1-way analysis of variance tests. Also, the groups did not differ in the proportion of female patients ($P=.53$) based on a Fisher exact test.

The rs4906844 genotype is associated with a widespread reduction in cortical thickness that is more prominent in frontotemporal regions (Figure 2 and eTable 2) and is remarkably similar to the pattern of cortical thinning consistently observed in patients with schizophrenia vs healthy controls.15-17 We tested whether rs4906844 can account for this pattern of thinning by grouping patients with schizophrenia by genotype and, for each genotypic group, comparing cortical thickness between this subset of patients with schizophrenia and all controls. (Note that we did not group the controls by genotype because we found no significant SNP effect on cortical thickness among them.) We found that patients with schizophrenia who are homozygous for the minor allele (AA) show the most significant thinning, but heterozygotes (AG) show moderate thinning and homozygotes for the major allele (GG) show no significant thinning relative to controls (Figure 3). Therefore, this SNP explains virtually all the observed difference in cortical thickness between patients with schizophrenia and controls in our study sample, although it does not account for other structural differences, such as reduced brain and subcortical volumes in schizophrenia.

To characterize the specificity of the SNP effect on cortical thickness, we tested the association of rs4906844 in 2 other diagnostic groups. We found that the SNP was not significantly associated with average cortical thickness in patients with bipolar disorder ($P=.88$; $\beta=-.002$; $n=97$) or healthy controls ($P=.13$; $\beta=0.013$; $n=181$) despite similar sample sizes and thus comparable power to detect an association (Figure 4). Furthermore, in a combined sample of patients with schizophrenia and controls, the SNP × diagnosis interaction $P$ value is significant ($P=1.56 \times 10^{-7}$) but less significant than the initial finding among patients with schizophrenia. In addition, the SNP effect is specific to cortical thickness because no significant association was observed between this SNP and other brain measures, including cortical surface area and intracranial, whole brain, subcortical, cerebellar, and ventricular volumes.

Finally, we tested whether rs4906844 is associated with increased risk of schizophrenia. We found that rs4906844 minor allele frequency in patients with schizophrenia (0.47) and controls (0.48) is not significantly different ($P=.91$), and the minor allele frequency is also comparable in patients with bipolar disorder (0.42).

Because cortical thickness has been associated with cognitive performance in healthy adults and adults with schizophrenia,29,30,41 we tested rs4906844 for association with cognition. Cognitive performance is significantly less heritable than brain structural measures and is associated with many neural factors not measured by cortical thickness, including cortical area and functional connectivity.42 Therefore, the effect of 1 SNP on cognition is likely to be small. Thus, to increase our power to detect an effect, we leveraged a MANOVA test of the association of rs4906844 with 17 tasks from the following tests: WASI,35 CVLT-II,33 and D-KEFS34 (Table 1).

\[ \beta = -0.069 \text{ mm per minor allele; } n=94 \] with average cortical thickness (Figure 1, eFigure 1, and eFigure 2), but in the second and third groups, no SNP associations were significant genome-wide (eFigure 3 and eFigure 4). Because these 2 SNPs are perfectly correlated in our sample of patients with schizophrenia ($r^2=1.0$), we arbitrarily focused the rest of our analysis on 1 SNP (rs4906844). This analysis is consistent with results for closely linked SNPs, including rs11633924. The fact that 2 SNPs on the genotyping chip exhibited association and were in strong linkage disequilibrium confirms that our association was not likely to result from a genotyping artifact. We found that patients with schizophrenia who had 0 copies of the minor allele of SNP rs4906844 (genotype GG, $n=26$) have a mean (SD) cortical thickness of 2.27 (0.09) mm, patients with 1 copy (AG, $n=45$) have a mean (SD) thickness of 2.20 (0.09) mm, and patients with 2 copies of the minor allele (AA, $n=23$) have a mean (SD) thickness of 2.13 (0.09) mm. These results represent a 3% reduction in cortical thickness per copy of the minor allele and a strikingly large effect size based on the comparison of patients with schizophrenia who are homozygous for the major and minor alleles (Cohen $d = (2.27-2.13)/0.09 = 1.56$). The 3 genotypic groups of patients with schizophrenia did not significantly differ in age ($P=.72$), full-scale IQ ($P=.59$), or symptom severity ($P=.93$) as assessed by the Positive and Negative Syndrome Scale based on 1-way analysis of variance tests. Also, the groups did not differ in the proportion of female patients ($P=.53$) based on a Fisher exact test.

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Finally, we tested whether rs4906844 is associated with increased risk of schizophrenia. We found that rs4906844 minor allele frequency in patients with schizophrenia (0.47) and controls (0.48) is not significantly different ($P=.91$), and the minor allele frequency is also comparable in patients with bipolar disorder (0.42).

Because cortical thickness has been associated with cognitive performance in healthy adults and adults with schizophrenia,29,30,41 we tested rs4906844 for association with cognition. Cognitive performance is significantly less heritable than brain structural measures and is associated with many neural factors not measured by cortical thickness, including cortical area and functional connectivity.42 Therefore, the effect of 1 SNP on cognition is likely to be small. Thus, to increase our power to detect an effect, we leveraged a MANOVA test of the association of rs4906844 with 17 tasks from the following tests: WASI,35 CVLT-II,33 and D-KEFS34 (Table 1).
These tasks assess higher-level executive skills with varying degrees of specificity; task performance has been shown to correlate with structure and function of the cortex.\(^{29,30,43}\)

The cognitive analysis included 196 patients with schizophrenia who had SNP genotype data and a complete set of measurements for all 17 neurocognitive measures. Briefly, MANOVA tests the association of the 17-measure profile with genotype by assessing the probability that a linear combination of these measures discriminates individuals based on the number of minor alleles of rs4906844 that they carried purely by chance. We used permutation tests to calculate the significance of the association. We controlled for the effect of age and sex in the MANOVA test and we found that rs4906844 was significantly associated (permuted \(P = .03\), Pillai=0.15) with the phenotypic cognitive performance profile composed of the 17 measures (Table 1).

We hypothesized that this SNP association with cognition was mediated by the SNP effect on cortical thickness. To test this hypothesis, we performed a secondary analysis with the subset of patients with schizophrenia (n=86) from the initial GWAS that had imaging, genotype, and cognitive data. A MANOVA test identified rs4906844 as significantly associated with the cognitive performance profile (\(P = .008\), Pillai=0.37), although this association was no longer significant (\(P = .14\), Pillai=0.28) when cortical thickness was included as a covariate. Moreover, a MANOVA test confirmed our prediction that rs4906844 is not associated with cognitive performance in patients with bipolar disorder (\(P = .49\), Pillai=0.10, n=178) or healthy controls (\(P = .39\), Pillai=0.07, n=368).

We performed post hoc linear regression tests for the association between rs4906844 minor allele count and each cognitive test measure in a slightly larger set of patients with schizophrenia (sample size range, 201-208) who had measurements for each test. Specifically, we predicted that the 14 cognitive tests that revealed significantly decreased performance in patients with schizophrenia vs healthy controls also would reveal decreased performance in patients with schizophrenia with more copies of the SNP minor allele. Indeed, we found that the SNP is associated with nominally decreased performance on 11 of the 14 cognitive tests, and collectively, these 11 tests involve more tests than would be expected by chance to occur based on a sign test if the measures are independent (\(P = .03\)). None of the SNP associations are statistically significant after correcting for multiple comparisons; however, the directions of the SNP effects are consistent with our hypothesis that reduced cortical thickness is associated with decreased cognitive performance.

On average, the effect size per minor allele on test performance in schizophrenia is approximately 6% of the effect size for a schizophrenia diagnosis (Table 2). For example, patients with schizophrenia who are homozygous for the minor allele (AA, n=46) perform 0.1 to 0.2 SDs below those homozygous for the major allele (GG, n=58) on the block design, matrix reasoning, and similarities measures of the WASI test. By contrast, patients with schizophrenia as a whole perform approximately 0.8 SDs worse on these 3 WASI tests than healthy controls. These results suggest that this SNP explains a small but consistent portion of the cognitive deficits that are associated with schizophrenia. Intriguingly, the most significant SNP association (nominal \(P = .03\)) is associated with a reduction in the measure of total repetition errors on the D-KEFS Verbal Fluency Test that accounts for the entire difference between patients with schizophrenia and healthy controls.

The SNP rs4906844 is located in the second intron of a putative protein-coding gene (LOC100128714) on chromosome 15q12 near (<500 kb) 2 maternally imprinted genes (ATP10A [OMIM 605855] and UBE3A [OMIM 601623]) and 1 nonimprinted gene (GABRB3...
In this study, we identified a common genetic variant that is associated with cortical thickness with genome-wide significance \( (P = 1.1 \times 10^{-8}) \), specifically in schizophrenia. This SNP \((rs4906844)\) accounts for virtually all the difference in cortical thickness between a sample of patients with schizophrenia and healthy controls, although the SNP does not explain other neuroanatomical differences between these groups, including reduced volumes of the cerebellum, hippocampus, thalamus, and amygdala.\(^{20}\) Also, \(rs4906844\) is modestly associated with neurocognitive performance among patients diagnosed as having schizophrenia, likely due to variation in cortical thickness associated with this SNP. Furthermore, the specificity of these associations for schizophrenia suggests differences in the genetic architecture that shapes brain structure in bipolar disorder.

Our finding that \(rs4906844\) does not increase the risk of schizophrenia is consistent with the observation that cortical thinning is not a strong intermediate phenotype for this disease. Although healthy adolescent siblings of individuals with childhood-onset schizophrenia have thinner cortices than controls,\(^{45}\) this difference disappears by 20 years of age, and healthy adult relatives of patients with schizophrenia show only trend-level cortical thinning compared with controls.\(^{15, 18, 44}\) Therefore, thinning may be related more to (ie, genetically and environmentally mediated by) disease processes and less to a genetic liability for schizophrenia.

The \(rs4906844\) genotype may interact with these disease processes to alter cortical thickness, possibly via epistasis with SNPs associated with schizophrenia or via interactions with “environmental” conditions characteristic of schizophrenia, such as use of antipsychotic medications and altered neurocognitive processing. Alternatively, \(rs4906844\) may act earlier to reduce cortical thickness and may contribute directly to schizophrenia onset because of the increased vulnerability of the brain to abnormal development. Various environmental challenges may contribute to this vulnerability, including living in an urban area\(^1\) or being an immigrant.\(^{49}\) Both of which are possible indicators of psychosocial adversity, as well as fetal risks.\(^1\) In either case, \(rs4906844\) would be expected to show no association with cortical thickness in patients without a schizophrenia diagnosis, which is what we observed in this study. However, future studies are needed to explore the specificity of the SNP association regarding cortical thickness in other patient groups with heritable cortical abnormalities, such as autism.

Cortical thinning is associated with decreased cognitive performance,\(^{20, 30, 41}\) so it is important to identify genes that contribute to variation in cortical thickness in health and disease. The \(rs4906844\) genotype is significantly associated with a multivariate profile implicating 17 neuropsychological tests that make various demands on executive skills. Moreover, this association is no longer significant if cortical thickness is included as a covariate, suggesting that the SNP effect on cognition is mediated by its effect on cortical structure. As predicted, \(rs4906844\) is significantly associated with nominally reduced performance on most cognitive tests, and the SNP is nominally associated with decreased total repetition errors on the D-KEFS Verbal Fluency Test. These results are consistent with those of a recent study\(^{29}\) in an independent set of individuals that demonstrated significant associations between several measures of executive function and cortical thinning in patients with schizophrenia and healthy controls.

However, patients with schizophrenia who are homozygous for the major allele and showed no significant cortical thinning relative to controls performed significantly worse on most cognitive tests than controls. This finding emphasizes the importance of factors not captured by differences in cortical thickness that contribute to decreased cognitive performance in schizophrenia. A limitation of this study is that some of the neurocognitive measures included in the analysis probe cognitive domains beyond executive function. For example, the CVLT-II and D-KEFS tests make demands on verbal ability, and the block design measure of the WASI test is sensitive to deficits in visuospatial and motor skills. Therefore, the SNP association we found may be driven in part by deficits in these other cognitive areas.

The \(rs4906844\) genotype is located within the putative gene \(LOC100128714\) that is expressed in the human brain; it codes for an amino acid sequence exceeding 96% conserved in great apes. The predicted protein structure contains no domains homologous to proteins with known function. The \(LOC100128714\) gene lies within the Prader-Willi and Angelman syndrome deletion region on chromosome 15q11-q13, and Prader-Willi syndrome is sometimes characterized by psychotic features, particularly in individuals with maternal uniparental disomy of chromosome 15.\(^{46, 47}\) Maternally derived duplications of 15q11-13 also may be a rare risk factor for schizophrenia and related psychoses.\(^{48}\) The \(LOC100128714\) gene has the potential to regulate 1 of the many imprinted and nonimprinted genes at this locus (including proximal genes \(ATP10A\), \(UBE3A\), and \(GABRB3\)) that have been implicated in neu-
rodevelopment and neuropsychiatric disease. For example, Ube3A recently has been implicated in regulating excitatory synapse development by targeting for degradation the synaptic proteins Arc and Ephexin. If rs4906844 indirectly regulates Ube3A, thereby altering synaptic development, then this SNP could contribute to the decreased dendritic spine density and resulting reductions to neuropil volume that have been associated with cortical thinning in schizophrenia.

Previous work in schizophrenia identified an enrichment of rare microdeletions on chromosomes 15q11.2 and 15q13.3, which are several megabases proximal and distal, respectively, to the region found in this study. Autism spectrum disorders also have been associated with 15q11-13; duplication of this genomic region may account for as many as 2% of cases, and a small 14-megabase de novo duplication has been identified in 1 patient with autism that spans LOC100128714, ATP10A, and GABRB3. The coincidence of copy number variations associated with schizophrenia and autism on chromosome 15q11-13 and across the genome suggests an overlapping genomic and developmental origin of these neuropsychiatric disorders. It will be interesting to learn whether rs4906844 or other SNPs in this region contribute to cortical phenotypes in autism.

Several GWASs have identified a handful of genetic loci consistently associated with schizophrenia, but no SNPs have been implicated on chromosome 15q12. Consistent with these results, we find no association between rs4906844 and schizophrenia diagnosis. Rather, we have identified an SNP that explains some of the neuroanatomical and cognitive heterogeneity within schizophrenia. Future studies should consider sequencing this genomic region in a large cohort of patients with schizophrenia to search for rare causal variants, and studies should explore the expression and imprinting of LOC100128714 and the function of the resulting protein.

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**Correction**

Incorrect Data. In the Original Article titled “Association of Genetic Variants on 13q12 With Cortical Thickness and Cognition in Schizophrenia” by Bakken et al, published in the August issue of the Archives (2011;68[8]:781-790), incorrect P values appear in the text, Table 1, and Figures 1 and 4 and the accompanying figure legends. In addition, the text in the “Results” section of the abstract on page 781 should read as follows: “Two closely linked genetic variants (rs4906844 and rs11633924) within the Prader-Willi and Angelman syndrome region on chromosome 13q12 showed a genome-wide significant association (P=1.08×10^{-8}) with average cortical thickness and are closely linked (r^2=0.7) to rs4906844.” The fourth sentence in the same paragraph should read as follows: “Two closely linked genetic variants (rs4906844 and rs11633924) within the Prader-Willi and Angelman syndrome region on chromosome 13q12 showed a genome-wide significant association (P=1.08×10^{-8}) with average cortical thickness and are closely linked (r^2=0.7) to rs4906844.” The fourth sentence in the same paragraph should read as follows: “Twenty-one SNPs were significantly associated (P<1×10^{-7}) but less significant than the initial finding among patients with schizophrenia.” Also, on page 787, in the left-hand column in the first full paragraph, the third sentence should read as follows: “Furthermore, in a combined sample of patients with schizophrenia and controls, the SNP × diagnosis interaction P value is significant (P=1.56×10^{-5}) but less significant than the initial finding among patients with schizophrenia.” On page 788, in the right-hand column, under the “Genotype” subheading, the third sentence should have read as follows: “A total of 597 198 SNPs passed quality control filters (call rate >95%, minor allele frequency >5%, Hardy-Weinberg disequilibrium P<1×10^{-8}) and were merged with HapMap 3 reference populations.” Also, on page 785, in the right-hand column in the first full paragraph, the third sentence should read as follows: “Furthermore, in a combined sample of patients with schizophrenia and controls, the SNP × diagnosis interaction P value is significant (P=1.56×10^{-5}) but less significant than the initial finding among patients with schizophrenia.” On page 781, in the left-hand column in the first full paragraph, the second sentence should read as follows: “Two closely linked genetic variants (rs4906844 and rs11633924) within the Prader-Willi and Angelman syndrome region on chromosome 13q12 showed a genome-wide significant association (P=1.08×10^{-8}) with average cortical thickness and are closely linked (r^2=0.7) to rs4906844.” The fourth sentence in the same paragraph should read as follows: “Five imputed SNPs show more significant association with cortical thickness than rs4906844 and are within 3.5 kb downstream of this SNP.”