

## Original Investigation

# Structural Brain Connectivity as a Genetic Marker for Schizophrenia

Marc M. Bohlken, MSc; Rachel M. Brouwer, PhD; René C. W. Mandl, PhD; Martijn P. Van den Heuvel, PhD; Anna M. Hedman, PhD; Marc De Hert, MD, PhD; Wiepke Cahn, MD, PhD; René S. Kahn, MD, PhD; Hilleke E. Hulshoff Pol, PhD

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**IMPORTANCE** Schizophrenia is accompanied by a loss of integrity of white matter connections that compose the structural brain network, which is believed to diminish the efficiency of information transfer among brain regions. However, it is unclear to what extent these abnormalities are influenced by the genetic liability for developing the disease.

**OBJECTIVE** To determine whether white matter integrity is associated with the genetic liability for developing schizophrenia.

**DESIGN, SETTING, AND PARTICIPANTS** In 70 individual twins discordant for schizophrenia and 130 matched individual healthy control twins, structural equation modeling was applied to quantify unique contributions of genetic and environmental factors on brain connectivity and disease liability. The data for this study were collected from October 1, 2008, to September 30, 2013. The data analysis was performed between November 1, 2013, and March 30, 2015.

**MAIN OUTCOME MEASURES** Structural connectivity and network efficiency were assessed through diffusion-weighted imaging, measuring fractional anisotropy (FA) and streamlines.

**RESULTS** The sample included 30 monozygotic twins matched to 72 control participants and 40 dizygotic twins matched to 58 control participants. Lower global FA was significantly correlated with increased schizophrenia liability (phenotypic correlation,  $-0.25$ ; 95% CI,  $-0.38$  to  $-0.10$ ;  $P = .001$ ), with 83.4% explained by common genes. In total, 8.1% of genetic variation in global FA was shared with genetic variance in schizophrenia liability. Local reductions in network connectivity (as defined by FA-weighted local efficiency) of frontal, striatal, and thalamic regions encompassed 85.7% of genetically affected areas. Multivariate genetic modeling revealed that global FA contributed independently of other genetic markers, such as white matter volume and cortical thickness, to schizophrenia liability.

**CONCLUSIONS AND RELEVANCE** Global reductions in white matter integrity in schizophrenia are largely explained by the genetic risk of developing the disease. Network analysis revealed that genetic liability for schizophrenia is primarily associated with reductions in connectivity of frontal and subcortical regions, indicating a loss of integrity along the white matter fibers in these regions. The reported reductions in white matter integrity likely represent a separate and novel genetic vulnerability marker for schizophrenia.

**Author Affiliations:** Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, the Netherlands (Bohlken, Brouwer, Mandl, Van den Heuvel, Hedman, Cahn, Kahn, Hulshoff Pol); Department of Neurosciences, Z.org KU Leuven-University Psychiatric Centre, Katholieke Unibersiteit, Leuven, Belgium (De Hert).

**Corresponding Author:** Marc M. Bohlken, MSc, Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, Heidelberglaan 100, 3584CX Utrecht, the Netherlands ([m.bohlken@umcutrecht.nl](mailto:m.bohlken@umcutrecht.nl)).

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Schizophrenia has been considered an illness of disrupted brain connectivity since its earliest descriptions.<sup>1-3</sup> Indeed, evidence from diffusion-weighted imaging studies<sup>4-8</sup> has confirmed that structural connectivity is affected in schizophrenia. Moreover, this disruption results primarily from disruptions in the network organization of the brain as a whole, the human connectome.<sup>9-12</sup>

Several studies<sup>13-20</sup> have found that white matter is affected not only in patients with schizophrenia but also in individuals at increased risk for the disease; however, other studies did not find significant differences between individuals at increased risk and healthy control participants.<sup>21,22</sup> The areas of white matter that are reduced in individuals at increased risk overlap with those found to be affected in patients, suggesting that familial, and possibly genetic, factors contribute to this effect.

Although the data so far suggest that a genetic component is involved in connectivity alterations and schizophrenia liability, it remains to be investigated whether the reported impaired connectivity is in fact genetically associated with the disorder.<sup>23</sup> Because schizophrenia liability is highly genetic<sup>24-26</sup> and measures of white matter diffusion, as well as various aspects of brain connectivity, are reported to have a genetic component in healthy individuals as well,<sup>27,28</sup> schizophrenia liability and connectivity could be driven by overlapping genetic factors. The discordant twin design is a powerful method to test this hypothesis.<sup>29-34</sup>

In this study, the central research question is whether white matter integrity is related to the genetic liability of developing schizophrenia. Data were acquired from 70 individual discordant and 130 individual control twins by T1-weighted and diffusion-weighted imaging. Global fractional anisotropy (FA) was used as a measure of white matter integrity. On the basis of a whole-brain diffusion tractography analysis, graph theoretical measures of global efficiency ( $E_G$ ) and local efficiency ( $E_L$ ) were subsequently calculated to study genetic effects on whole-brain network connectivity. With the use of structural equation modeling, genetic and environmental associations between schizophrenia and structural brain connectivity were estimated. A multivariate modeling approach was subsequently applied to investigate whether changes in other genetic markers for schizophrenia, such as white matter volume (WMV) and cortical thickness (CT),<sup>30,34</sup> contribute to schizophrenia liability independent of brain connectivity parameters.

## Methods

### Sample Description

This newly acquired Utrecht twin cohort (U-TWIN) consists of 70 twins with discordance for schizophrenia and 130 control twins (see Table 1 for demographics of the sample). The data for this study were collected from October 1, 2008, to September 30, 2013. The data analysis was performed between November 1, 2013, and March 30, 2015. For details of psychiatric assessment, see eTable 1 in the Supplement. The control twins were selected to match the discordant twins on age, handed-

ness, and parental educational level. There were more males in the discordant twin group compared with the control twins, which was corrected for statistically. Control twins were excluded if they ever met criteria for a psychotic or manic disorder or substance dependence, had a first-degree relative with schizophrenia, or were diagnosed as having a neurologic disorder. Zygosity of all twins was determined through testing polygenic genetic markers. The zygosity of incomplete pairs was known from participation in earlier studies. The Medical Ethical Committee of the University Medical Center Utrecht approved this study, and the experiments were in accordance with the Declaration of Helsinki. All participants gave their written informed consent.

### Data Acquisition

The scan protocol included a T1-weighted scan and 2 diffusion-weighted scans.<sup>12</sup> All scans were acquired using an Achieva scanner (Philips Healthcare) operating at 3T. For detailed information on scan acquisition, preprocessing, diffusion profile modeling,<sup>35</sup> and calculation of global brain measures, such as WMV<sup>28</sup> and CT, see the eMethods in the Supplement.

### Connectivity Measures

As an indication of global white matter integrity, a measure of global FA was obtained by averaging the FA values over all voxels within the white matter skeleton (FA >0.2), as obtained by analysis with Tract-Based Spatial Statistics software, version 4.1.7 (FSL; <http://fsl.fmrib.ox.ac.uk>). For calculating structural network connectivity parameters, whole-brain diffusion tensor imaging was applied in each individual and was overlaid with 82 segmented gray matter regions (obtained using FreeSurfer software, version 5.1 [Martinos Center for Biomedical Imaging, at the Laboratory for Computational Neuroimaging]) to capture all connections between them. Only connections found in more than 50% of participants were retained,<sup>36</sup> resulting in a single-group connectivity matrix that contained 850 connections. The  $E_G$  was calculated over the whole network, and the  $E_L$  was calculated for each gray matter region using FA-weighted, number of streamlines (NOS)-weighted, and unweighted (binary) matrices.<sup>37</sup> The  $E_G$  is a mathematical definition of the level of integration of all nodes (gray matter regions) included in the network. The  $E_L$  is a mathematical measure of fault tolerance, that shows how efficient the organization of connections among direct neighbors of a node remains after hypothetically removing it (eMethods in the Supplement). Therefore, unweighted efficiency measures are most informative about the topology of connections, whereas weighted efficiency measures are also informative about the connection strengths.<sup>9</sup> In the context of FA-weighted connectivity, connections with higher mean FA values are interpreted to have higher connection strength.

The mean FA value over each connection was obtained to perform structural connectivity analysis at the level of single connections. For each brain region, the mean FA value over all connections with this region was calculated as a measure of mean FA-weighted connection strength. Two monozygotic control twins were excluded from the structural connectivity analysis as based on the outlier analysis (mean FA >4 SDs from the mean).

Table 1. Demographic Characteristics of the Study Participants<sup>a</sup>

Characteristic	Monozygotic Twins			Dizygotic Twins		
	Patients (n = 16)	Co-twins (n = 14)	Controls (n = 72)	Patients (n = 21)	Co-twins (n = 19)	Controls (n = 58)
Sex, M/F	13/3 (81.3/18.8)	9/5 (64.3/35.7)	34/38 (47.2/52.8)	13/8 (61.9/38.1)	14/5 (73.7/26.3)	27/31 (46.6/53.4)
Age, mean (SD), y	35.3 (12.9)	36.1 (14.0)	36.7 (14.1)	37.6 (11.2)	37.9 (12.2)	35.4 (13.4)
Handedness, right/nonright	14/2 (87.5/12.5)	12/2 (85.7/14.3)	66/6 (91.7/8.3)	20/1 (95.2/4.8)	16/3 (84.2/15.8)	11/47 (19.0/81.0)
Educational level, mean (SD), y	14.0 (2.6)	12.8 (2.8)	14.5 (2.0)	12.5 (2.6)	14.2 (1.6)	14.4 (2.3)
Parental educational level, mean (SD), y	13.2 (3.1)	13.4 (2.8)	12.7 (2.6)	14.0 (2.7)	13.3 (2.8)	12.5 (2.9)
History of smoking (yes/no)	10/6 (62.5/37.5)	9/5 (64.3/35.7)	11/61 (15.3/84.7)	13/8 (61.9/38.1)	9/10 (47.4/52.6)	15/43 (25.9/74.1)
No. of cigarettes smoked per day, mean (SD)	20.0 (8.1)	15.2 (8.4)	10.5 (8.20)	21.9 (10.6)	11.9 (9.2)	9.5 (6.3)
Alcohol use (yes/no)	7/9 (43.8/56.3)	9/5 (64.3/35.7)	48/24 (66.7/33.3)	9/12 (42.9/57.1)	14/5 (73.7/26.3)	40/18 (69.0/31.0)
Alcohol use, mean (SD), U/wk	13.6 (18.9)	15.0 (16.4)	6.4 (4.4)	9.2 (7.5)	9.3 (7.7)	10.1 (7.3)
Age at onset, mean (SD), y	22.5 (5.9)	...	...	19.6 (4.7)	...	...
Duration of illness, mean (SD), y	12.8 (10.2)	...	...	18.2 (11.6)	...	...
Type of antipsychotic medication						
Typical	1	...	...	2	...	...
Atypical	14	...	...	14	...	...
Both	0	...	...	4	...	...
None	1	...	...	1	...	...
Chlorpromazine equivalent, mean (SD), mg/d						
Typical	600 (0)	...	...	450 (212)	...	...
Atypical	528 (398)	...	...	489 (360)	...	...
Both	...	...	...	818 (311)	...	...
PANSS	50.9 (22.2)	...	...	45.4 (13.3)	...	...

Abbreviation: PANSS, Positive and Negative Syndrome Scale.

<sup>a</sup> The sample included 12, 2, and 36 complete pairs and 2, 0, and 0 incomplete pairs of discordant, concordant, and control monozygotic twins, respectively, and 19, 0, and 27 complete pairs and 2, 0, and 4 incomplete pairs of

discordant, concordant, and control dizygotic twins, respectively. Data are presented as number (percentage) of study participants unless otherwise indicated.

<sup>b</sup> Ellipses indicate data not applicable.

## Genetic Modeling

The twin model was implemented using structural equation modeling in which the contributions of additive genetic effects, shared environmental effects, and unique environmental effects to trait variation and covariation are estimated by maximum likelihood. The twin model was used to calculate the heritability of all brain measures and the associations with disease liability. The critical threshold and heritability for the underlying liability for schizophrenia were not based on this sample because participant inclusion was not population based. Therefore, the prevalence and heritability of schizophrenia were fixed to population values; prevalence was set to 1%, and heritability was set to 81%. Effects of shared environment on schizophrenia liability were set to 11%, and effects of unique environment were set to 8%.<sup>24</sup> To express whether connectivity and schizophrenia liability were influenced through common genes, the additive genetic effects ( $r_{ph-a}$ ) on the total phenotypic correlation ( $r_{ph}$ ) were calculated. This measure can be described as the correlation between 2 variables that would be observed if only additive genetic effects are taken into account.<sup>38</sup> The unique environmental effects on the  $r_{ph}$  ( $r_{ph-e}$ ) was calculated to ex-

press correlation through environmental factors. For detailed description on model fitting,<sup>34,39</sup> see the eMethods in the Supplement.

## Parameter Simulation and Power Analysis

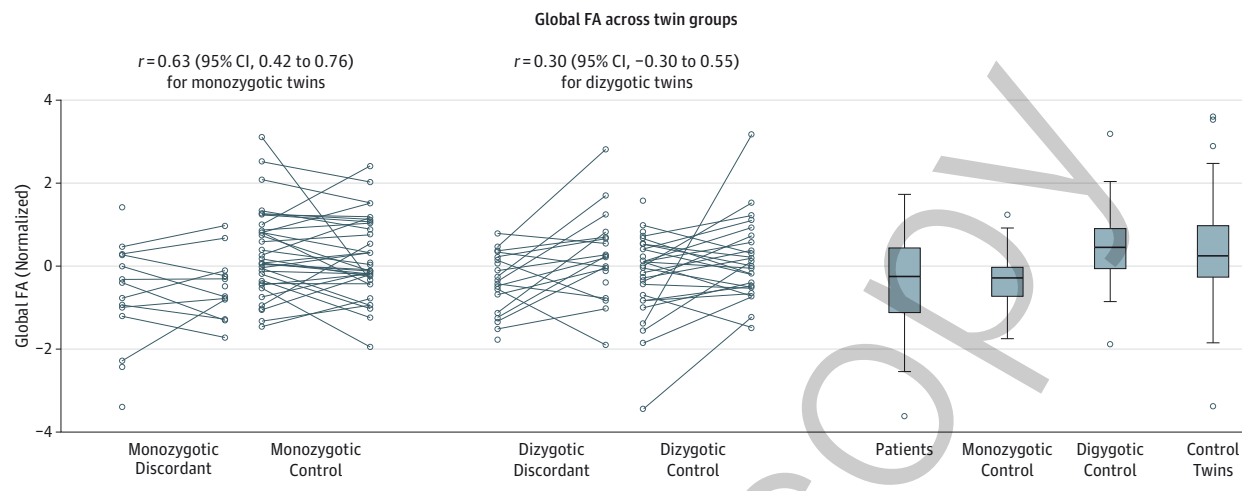
To ensure that fixing the prevalence and heritability estimates of schizophrenia in our genetic modeling did not influence our results, a simulation analysis was performed that also allowed for a post hoc power calculation (eMethods in the Supplement).

## Results

### Global Structural Connectivity

Using a bivariate model that incorporated additive genetic and unique environmental effects on global FA, the heritability of global FA was estimated at 0.63 (95% CI, 0.48-0.74; shared environmental effects could be dropped;  $P = .006$  for shared and unique environmental effects). In addition, monozygotic and dizygotic within-twin correlations support a strong effect of additive genetics (Figure 1). Lower global FA was signifi-

Figure 1. Global Fractional Anisotropy (FA) Across Twin Groups



On the y-axis, the normalized FA values are given per study participant. Normalized values were obtained by first performing linear regression for age, handedness, and sex, followed by a normalization of the mean (SD) on the residuals of the regression. On the x-axis, the results are shown per group. In the discordant groups, the affected twin is shown first, and the co-twin is shown second. In the control groups, the order of twin 1 and twin 2 is assigned

at random. The final 4 boxplots show the mean connectivity values for patients (mean [SD] FA, 0.428 [0.020]), monozygotic co-twins (mean [SD] FA, 0.431 [0.014]), dizygotic co-twins (mean [SD] FA, 0.442 [0.020]), and control twins (mean [SD] FA, 0.441 [0.018]). The length of the boxplot whiskers is 1.5 times the interquartile range.

cantly phenotypically correlated with increased schizophrenia risk ( $r_{ph} = -0.25$ ; 95% CI,  $-0.38$  to  $-0.10$ ;  $P = .001$ ). This correlation was largely determined through genetic factors shared between global FA and schizophrenia liability ( $r_{ph-a} = -0.21$ ; 95% CI,  $-0.35$  to  $-0.05$ ;  $P = .01$ ), with 83.4% of the association between global FA and schizophrenia liability explained through shared genes. Furthermore, 8.1% of the total genetic variance in global FA was shared with genetic variance for schizophrenia liability. Compared with the control twins, global FA was reduced by 2.9% (Cohen  $d = 0.67$ ) in patients with schizophrenia, reduced by 2.1% (Cohen  $d = 0.59$ ) in monozygotic co-twins, and increased by 0.4% (Cohen  $d = 0.08$ ) in dizygotic co-twins (Figure 1).

Unweighted binary  $E_G$  was substantially heritable (heritability, 0.64; 95% CI, 0.48-0.73; shared environmental effects on  $E_G$  could be dropped;  $P = .02$ ). Unweighted binary  $E_G$  was not altered in schizophrenia ( $r_{ph} = -0.03$ ; 95% CI,  $-0.18$  to 0.11;  $P = .65$ ). The heritability of FA-weighted  $E_G$  for FA was 0.69 (95% CI, 0.53-0.79; shared environmental effects on  $E_G$  for FA could be dropped;  $P = .004$ ). The  $E_G$  for FA was reduced in schizophrenia ( $r_{ph} = -0.22$ ; 95% CI,  $-0.36$  to  $-0.07$ ;  $P = .004$ ), which was attributable to shared genetic factors ( $r_{ph-a} = -0.19$ ; 95% CI,  $-0.34$  to  $-0.04$ ;  $P = .02$ ), explaining 88.9% of their association. Neither additive genetic effects nor shared environmental effects were estimated to be significant in NOS-weighted  $E_G$ ; it was also not significantly associated with schizophrenia liability. For model fit statistics of analyses performed in this section, see eTable 2 in the Supplement.

### Regional and Local Structural Connectivity

In 46 gray matter regions, lower FA-weighted  $E_L$  was significantly correlated with increased schizophrenia liability. Of these regions, 14 had a significant genetic association, and 7

had a significant association through environmental factors (Figure 2; eTables 3, 4, and 5 in the Supplement). Of all 850 individual FA-weighted structural connections, 160 (18.8%) had a significant  $r_{ph}$  for schizophrenia and FA after false discovery rate correction. Of these connections, 31 (19.4%) had a significant  $r_{ph-a}$  for schizophrenia and FA, and 8 (5.0%) had a significant  $r_{ph-e}$  for schizophrenia and FA (Figure 2). For additional results based on mean FA-weighted connection strength, see eFigure 1 in the Supplement. Unweighted binary  $E_L$  and NOS-weighted  $E_L$  connectivity measures did not have significant alterations after false discovery rate correction.

### Modeling of Other Genetic Markers

With the use of a bivariate model that incorporated additive genetic and unique environmental influences on WMV, the heritability of WMV was 0.85 (95% CI, 0.79-0.89; shared environmental effects could be dropped;  $P < .001$  for shared and unique environmental effects). Lower WMV was significantly correlated with increased schizophrenia liability ( $r_{ph} = -0.15$ ; 95% CI,  $-0.29$  to 0.00;  $P = .04$ ); this correlation could not be significantly attributed to genetic factors ( $r_{ph-a} = -0.07$ ; 95% CI,  $-0.22$  to 0.08;  $P = .38$ ) whereas a small part was influenced by environmental factors ( $r_{ph-e} = -0.05$ ; 95% CI,  $-0.09$  to 0.01;  $P = .02$ ). The heritability of CT was 0.77 (95% CI, 0.67-0.83; shared environmental effects on CT could be dropped;  $P = .004$  for shared and unique environmental effects). Lower CT was correlated with increased schizophrenia liability ( $r_{ph} = -0.23$ ; 95% CI,  $-0.37$  to  $-0.09$ ;  $P = .002$ ) and could be significantly attributed to genetic factors ( $r_{ph-a} = -0.21$ ; 95% CI,  $-0.35$  to 0.06;  $P = .006$ ); environmental factors were not significant ( $r_{ph-e} = -0.03$ ; 95% CI,  $-0.08$  to 0.02;  $P = .23$ ). For model output statistics of the analyses above, see eTable 2 in the Supplement.

Figure 2. Structural Fractional Anisotropy (FA)-Weighted Local Efficiency in Schizophrenia

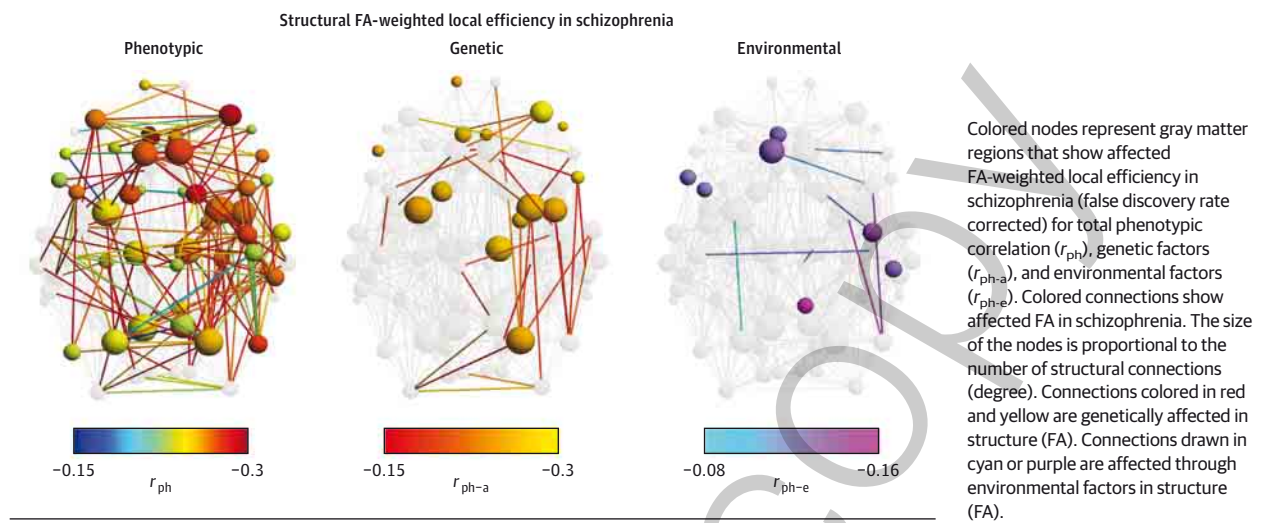
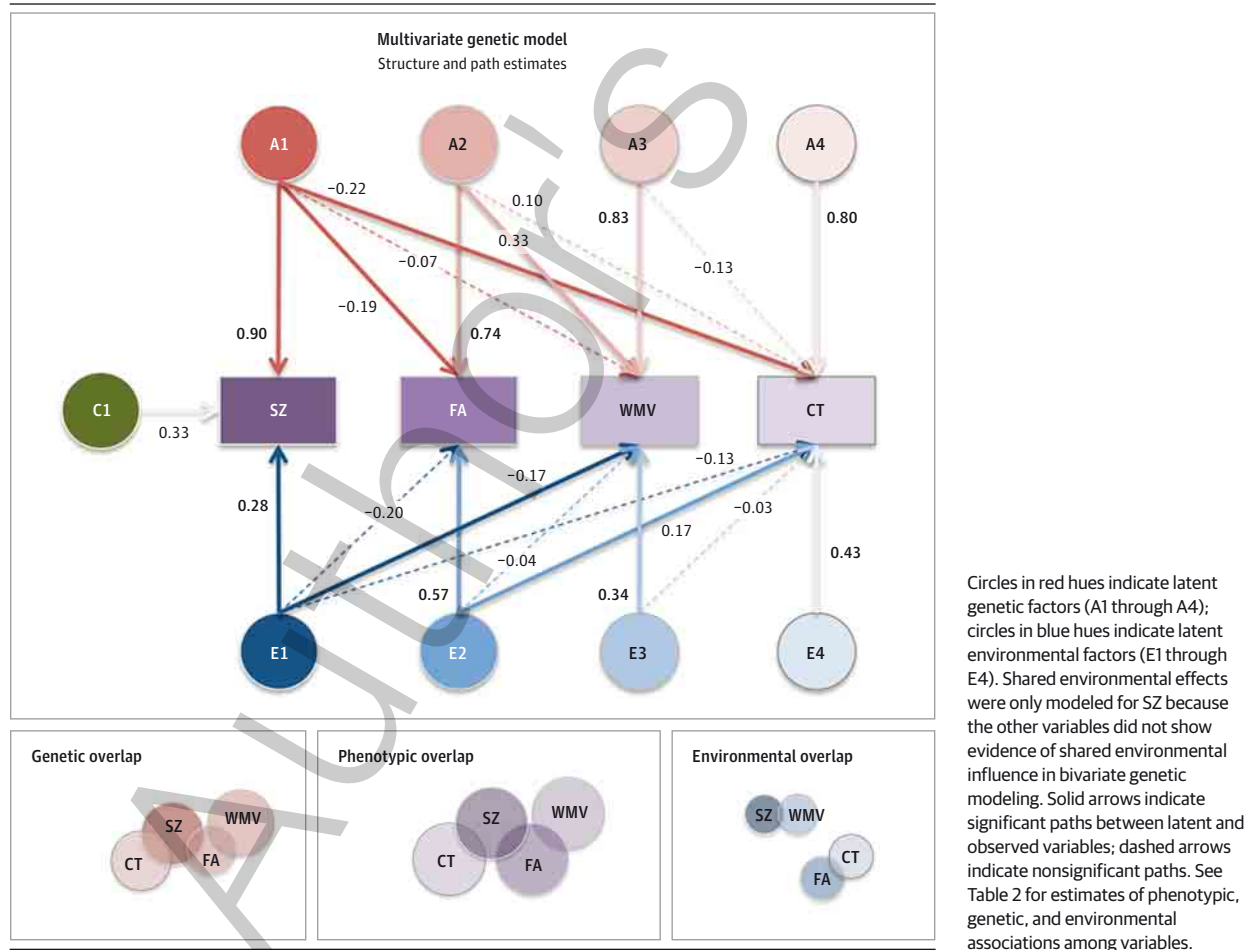


Figure 3. Multivariate Genetic Model Incorporating Schizophrenia Liability (SZ), Global Fractional Anisotropy (FA), Cortical Thickness (CT), and White Matter Volume (WMV)



A multivariate model was fitted to study genetic and environmental contributors to global structural connectivity and genetic markers, such as WMV and CT, in relation to schizophrenia liability (Figure 3). Global FA and CT were not genetically

correlated; global FA and WMV shared a genetic association. Environmental correlations were observed between schizophrenia and WMV and between global FA and CT (Table 2).

**Table 2. Multivariate Modeling of Phenotypic, Genetic, and Environmental Associations Among All Major Brain Variables and SZ<sup>a</sup>**

Multivariate Modeling	Correlation (95% CI)			
	SZ	FA	WMV	CT
<b>Phenotypic Associations Among Variables</b>				
SZ	... <sup>b</sup>	...	...	...
FA	-0.24 (-0.38 to -0.09)	...	...	...
WMV	-0.12 (-0.27 to 0.02)	0.30 (0.15 to 0.43)	...	...
CT	-0.24 (-0.37 to -0.09)	0.25 (0.10 to 0.39)	-0.06 (-0.21 to 0.10)	...
<b>Genetic and Environmental Associations Among Variables</b>				
SZ	...	-0.06 (-0.13 to 0.02)	-0.05 (-0.09 to -0.01)	-0.04 (-0.09 to 0.02)
FA	-0.18 (-0.32 to -0.02)	...	0.01 (-0.06 to 0.09)	0.13 (0.05 to 0.24)
WMV	-0.07 (-0.22 to 0.08)	0.28 (0.12 to 0.42)	...	0.01 (-0.05 to 0.06)
CT	-0.20 (-0.34 to -0.05)	0.13 (-0.05 to 0.28)	-0.06 (-0.22 to 0.10)	...

Abbreviations: CT, cortical thickness; FA, fractional anisotropy; SZ, schizophrenia liability; WMV, white matter volume.

<sup>a</sup> The phenotypic association between WMV and SZ does not reach significance in this multivariate model, whereas it does in the bivariate model. This finding is likely owing to the relatively high association between WMV and FA, explaining variance in WMV that would otherwise be directly attributed to SZ.

<sup>b</sup> Ellipses indicate data not applicable.

Because both global FA and CT were estimated to share genes with schizophrenia liability and the 2 traits were correlated, an additional bivariate genetic model for schizophrenia and FA was run in which the variance due to CT was regressed out of the global FA variable. With regression for CT, global FA remained significantly genetically associated with schizophrenia liability ( $r_{\text{ph-a}} = -0.18$ ; 95% CI, -0.34 to 0.01;  $P = .04$ ) (eTable 6 in the Supplement). To statistically test the independence of genetic components for global FA and CT, a trivariate model was fitted that incorporated global FA, CT, and schizophrenia. Constraining the  $a_{(23)}$  component to 0 significantly deteriorated the model fit ( $P = .03$ ) (eFigure 2 in the Supplement). Thus, genetic variance loaded on schizophrenia liability by global FA and CT is best explained by 2 independent genetic factors.

### Regional Overlap Between Connectivity and CT Results

The overlap among local regions in which schizophrenia liability is genetically associated with FA-weighted  $E_L$  and CT was limited ( $\chi^2 = 0.39$ ;  $P = .53$ ), suggesting no one-to-one association between global FA and CT in schizophrenia. For an overview of the genetic associations between local CT and schizophrenia liability, see eTable 7 in the Supplement. Only the right insula had this overlap; trivariate modeling confirmed that 2 independent genetic factors also best explained this overlap ( $P = .004$ ).

### Parameter Simulation and Post Hoc Power Analysis

Fixing the heritability and prevalence of schizophrenia did not bias the estimates for heritability of global FA, phenotypic, and genetic correlations (eTable 8 in the Supplement). The fraction of significant estimates in these models had sufficient power to detect genetic influences. The environmental correlations varied more and were not consistently detected (eTable 8 in the Supplement).

## Discussion

We investigated whether schizophrenia liability and white matter integrity share common genes. The main finding is that reductions in white matter integrity have genetic overlap with

schizophrenia disease liability. This finding suggests that genes that are relevant for (the development of) structural brain connections are partly overlapping with genes for schizophrenia. Local connectivity of frontal and striatal brain regions encompassed the greatest proportion (85.7%) of genetically affected brain regions.

Global white matter integrity had a significant genetic association with schizophrenia liability, with 83.4% of the association explained by common genes. Thus, the often reported reductions in white matter integrity<sup>4,5,12</sup> can largely be explained as a genetic liability for schizophrenia. This result was also reflected in the whole-brain FA-weighted  $E_L$  and  $E_G$ . Efficiency measures of unweighted and NOS-weighted networks were not significantly affected in schizophrenia and were not genetically associated with increased liability. This finding indicates that our main finding is specific to a loss of integrity along white matter fibers because alterations in unweighted and NOS-weighted measures would have indicated genes involved in the topology and thickness of white matter fibers, respectively.<sup>9</sup>

Overall, 50.0% of all genetically affected regions were situated in the frontal cortex. Decreases in white matter integrity connecting the frontal cortex with other brain regions have been suggested as a genetic marker for schizophrenia, which is consistent with our findings.<sup>40</sup> Our results suggest the involvement of connections with subcortical structures, such as the striatum and thalamus (encompassing 29.0% of genetically affected structures). Although the high connection density in frontal and subcortical regions may have influenced these findings, they are consistent with the hypothesis that impairments in frontostriatal connections are critical to the pathogenesis of schizophrenia.<sup>41-43</sup> Neuroimaging studies have found evidence of disturbed connectivity in these regions in relation to aberrant salience deficits, reward, and positive and negative symptoms in schizophrenia,<sup>44-46</sup> with those at increased familial risk of schizophrenia having abnormalities in frontostriatal white matter integrity.<sup>47</sup>

A number of (primarily frontal) regions had a significant environmental association between schizophrenia liability and local connectivity. This finding indicates that decreases in these regions occur only in patients (not in co-twins) despite significant heritability, suggesting that disease-specific factors are also

influencing white matter connections in schizophrenia. However, when power limitations for detecting environmental effects are considered, these results should be interpreted with caution.

Multivariate modeling was applied to further investigate how the genetic association between white matter integrity and schizophrenia liability is related to changes in other known genetic markers, such as WMV and CT. This model confirmed CT and schizophrenia liability to be influenced by common genes.<sup>34</sup> More important, although white matter integrity and CT were positively correlated, confirming earlier findings,<sup>48</sup> genes were not involved in this association. Our results indicate that 2 separate genetic factors contribute to schizophrenia liability, one shared with global CT and another with white matter integrity. At the local level, our results also support the solution with 2 independent genetic factors. One of these genetic factors possibly contributes to risk at the neuronal level situated in the gray matter with connecting axons in white matter. Schizophrenia-associated reductions in CT may originate from a loss of dendritic spines on pyramidal neurons in cortical layer III, which may be related to known schizophrenia risk genes.<sup>49</sup>

The other genetic factor could contribute to risk at the level of the supporting tissue. Oligodendrocyte dysfunction is hypothesized to contribute to schizophrenia risk through hypomyelination and a loss of axonal metabolic support.<sup>50,51</sup> Oligodendrocyte gene sets implicated in lipid metabolism and oxidation reduction were found to be associated with schizophrenia risk, suggesting that these gene sets may be causally related to the illness.<sup>52</sup> The observed correlation between CT and white matter integrity in schizophrenia may indicate that dendritic abnormalities and oligodendrocyte dysfunction influence each other. A longitudinal measurement may help to gain a better understanding of the temporal aspect of these associations.

Future discordant twin research may focus on testing causal hypotheses regarding these genetic factors in relation to schizophrenia, as was recently applied in a large pan-European twin cohort.<sup>53</sup> Because functional connectivity may also be genetically implicated in schizophrenia liability,<sup>54</sup> inclusion of such measures in multivariate genetic models may provide new insights regarding the still limited understanding of associations between brain structure and function in schizophrenia.<sup>55</sup>

In previous studies,<sup>30,33</sup> WMV reductions were genetically associated with schizophrenia liability. In this study, the genetic association between WMV and schizophrenia liability was negative but not significant. Instead, a small environmental component was estimated. A factor that may have contributed is the shorter mean illness duration and younger age (approximately 5 years) of the monozygotic discordant twins

compared with the previous cohort.<sup>30</sup> Because patients with schizophrenia have excessive WMV increases<sup>56</sup> up to 32 years of age and white matter integrity may be altered before disease onset,<sup>20</sup> the lack of a significant genetic effect in this younger cohort may be related to a difference in neurodevelopment, where decreases in white matter integrity are preceded by decreases in volume.

Some limitations should be taken into consideration when interpreting the findings of this study. We report a shared set of additive genes that influence both schizophrenia risk and white matter integrity. However, other mechanisms, including epistasis, linkage disequilibrium, phenotypic causality, and environmentally mediated effects of one genetically influenced trait on another, could also explain these findings.<sup>57,58</sup> We cannot rule out the possibility of such effects because the dizygotic co-twins did not have a significant change in global FA whereas the monozygotic co-twins were phenotypically more similar to patients. In fact, global FA was slightly but not significantly increased in dizygotic co-twins compared with controls. On the basis of genetic liability, mild reductions were expected in that group. This is possibly because a large number of the dizygotic co-twins were sufficiently under the liability threshold to show affected white matter. Some literature even suggests a protective mechanism in siblings of patients to explain higher white matter connectivity.<sup>17</sup> Still, it is unlikely that this genetic correlation is entirely explained by nonadditive factors. Because the dizygotic correlation was approximately half of the monozygotic correlation, global FA is likely under the strong influence of additive genetic factors. We also used fixed heritability estimates based on the literature because we could not perform population sampling (heritability for schizophrenia, 81%).<sup>24</sup> Post hoc simulation analysis confirmed that this did not bias the estimation of genetic and environmental sources of covariation. Furthermore, reanalysis of the main variables using a fixed heritability of 64%<sup>25</sup> did not lead to different findings.

## Conclusions

Decreases in white matter integrity are influenced by genes that confer liability to develop schizophrenia. Our results suggest that independent genetic pathways lead to gray and white matter abnormalities in schizophrenia. The white matter findings reported here could be related to genetic mechanisms that control myelination, particularly affecting connectivity of frontal and subcortical regions. Therefore, white matter integrity should be considered a primary phenotype for linking genes to biological pathways that contribute to the development of schizophrenia.

### ARTICLE INFORMATION

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**Study concept and design:** Bohlken, Hedman, De Hert, Kahn, Hulshoff Pol.

**Acquisition, analysis, or interpretation of data:** Bohlken, Brouwer, Mandl, Van den Heuvel,

Hedman, Cahn, Hulshoff Pol.

**Drafting of the manuscript:** Bohlken, Hedman, Hulshoff Pol.

**Critical revision of the manuscript for important intellectual content:** All authors.

**Statistical analysis:** Bohlken, Brouwer, Van den Heuvel.

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