Utilizing Mutual Information Analysis to Explore the Relationship Between Gray and White Matter Structural Pathologies in Schizophrenia

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Schizophrenia has been characterized as a neurodevelopmental disorder, with structural brain abnormalities reported at all stages. However, at present, it remains unclear whether gray and white matter abnormalities represent related or independent pathologies in schizophrenia. In this study, we present findings from an integrative analysis exploring the morphological relationship between gray and white matter in 45 schizophrenia participants and 49 healthy controls. We utilized mutual information (MI), a measure of how much information two variables share, to assess the morphological dependence between gray and white matter in three segments of the corpus callosum, and the gray matter regions these segments connect: (1) the genu and the left and right rostral middle frontal gyrus (rMFG), (2) the isthmus and the left and right superior temporal gyrus (STG), (3) the splenium and the left and right lateral occipital gyrus (LOG). We report significantly reduced MI between white matter tract dispersion of the right hemispheric callosal connections to the STG and both cortical thickness and area in the right STG in schizophrenia patients, despite a lack of group differences in cortical thickness, surface area, or dispersion. We believe that this reduction in morphological dependence between gray and white matter may reflect a possible decoupling of the developmental processes that shape morphological features of white and gray matter

early in life. The present study also demonstrates the importance of studying the relationship between gray and white matter measures, as opposed to restricting analyses to gray and white matter measures independently.

Key words: schizophrenia/morphology/gray matter/white matter/mutual information

Introduction

Gray and white matter structural pathologies are hallmark findings in schizophrenia that are observed at all stages of the disorder. In neuroimaging studies, gray matter pathologies commonly manifest as reductions in gray matter volume, usually the result of cortical thinning and surface area loss in parietal, temporal, and frontal regions.^{1,2} In contrast, white matter pathologies include widespread reductions in fractional anisotropy (FA), a measure of tissue microstructure, in white matter connections that include the corpus callosum, cingulum bundle, superior longitudinal fasciculus, and others.^{3,4} Interestingly, the neurobiological mechanisms proposed to explain neuroimaging findings tend to focus on a single pathology. For example, gray matter loss is thought to be related to a reduction in dendritic spines and synapses, or

apoptosis.^{5,6} Alterations in white matter measures, on the other hand, are thought to be related to aberrant myelination, axonal damage, or immune activation.^{7,8} However, at present, it remains unclear whether these gray and white matter abnormalities represent related or independent pathologies in schizophrenia.

A few studies have explored relationships between gray and white matter structural pathologies. Three previous studies report significant associations between several gray and white matter measures, but with little overlap among findings.^{9–11} These studies correlated average gray matter measures within a given region of interest (ROI), such as cortical thickness or surface area, with average FA measures of nearby or connecting white matter. While this work provides an important first step, there are a number of limitations. The use of correlative measures requires researchers to work with regional averages. A single white matter tract, however, can exhibit distinct patterns of FA variation reflecting changes in the anatomical environment along the bundle. The same is true for gray matter measures in that cortical thickness is linked to underlying cytoarchitecture, which can be highly variable across an ROI. In both cases, taking an average potentially results in a loss of important information.

Another approach is to examine morphological relationships between white matter tracts and the cortical gray matter areas to which they project. While it may be relatively apparent that cortical gray matter morphology is related to the underlying structural geometry of white matter tracts, the exact relationship is still unknown. Measures of gray matter morphology are widely available, yet there are a limited number of measures to describe white matter morphology. Recently, Savadjiev et al.¹² introduced a method called tract dispersion. This measure provides specific information about the physical structure and geometrical organization of white matter tracts by computing the extent to which white matter fibers deviate from being parallel (eg, fanning fibers). Three studies employing an earlier version of this method report significant reductions in white matter dispersion in the genu of the corpus callosum in chronic schizophrenia and adolescent-onset schizophrenia, and in those genetically at-risk for schizophrenia.^{13–15}

Savadjiev et al.¹² applied tract dispersion along with mutual information (MI) to quantify the relationship between gray and white matter morphology in autism spectrum disorder. MI provides information about the extent to which the geometrical structure of the white matter tract is informative about the morphological structure of the cortical area it connects to, and vice versa. MI provides two significant advantages over correlative approaches. First, it is based upon the distribution of given gray and white matter variables, and it thereby utilizes all information along the gray cortical surface and white matter tract, avoiding the use of regional averages. Second, MI allows for the investigation of possible nonlinear relationships. Thus, the use of MI, instead of

correlative approaches, provides a unique way to analyze localized morphological information when investigating the interaction of white matter tracts and the gray matter cortical regions they connect.

The goal of this study is to use MI to investigate whether control subjects and patients with schizophrenia exhibit different morphological relationships between gray and white matter. We will use MI to quantify the degree of dependency between gray and white matter morphological features in healthy controls, and determine whether the dependency is altered in individuals with schizophrenia. To accomplish this goal, we calculated vertex-based measurements of white matter tract dispersion and gray matter cortical thickness, cortical surface area, and cortical curvature. We focus on three segments of the corpus callosum defined by the gray matter regions of interest they connect: (1) bilateral rostral middle frontal gyrus (rMFG), (2) bilateral superior temporal gyrus (STG), and (3) bilateral lateral occipital gyrus (LOG). We chose these regions based on previous literature that report gray matter pathology in frontal and temporal regions and white matter abnormalities in the corpus callosum.^{15,16} Earlier studies of white matter dispersion reported differences between schizophrenia populations and controls in the corpus callosum^{13–15} and we feel that the investigation of interhemispheric structural connectivity between bilaterally represented cortical regions is the most parsimonious way to investigate morphological gray/white matter relationships. In addition to the methodological motivations, Kelly et al.¹⁷ recently conducted the largest meta-analysis of white matter in schizophrenia patients, with data from over 4000 individuals. The authors showed that the corpus callosum, in particular, the genu and body, exhibit some of the largest reductions in effect sizes between groups, demonstrating that it may be a common structural alteration in schizophrenia pathophysiology.¹⁷ We believe that this approach will help increase our understanding of the relationship between gray and white matter pathologies in schizophrenia.

Methods

Participants

The sample, collected as part of the Boston Center for Intervention Development and Applied Research (CIDAR) study, included 24 recent-onset schizophrenia patients and 25 chronic patients, as well as 45 healthy controls matched to recent-onset ($n = 23$) and chronic ($n = 22$) patient groups. The study was approved by local IRB committees at Harvard Medical School, Beth Israel Deaconess Medical Center, Massachusetts General Hospital, Brigham and Women's Hospital, and the Veteran Affairs Boston Healthcare System. All study participants (or legal guardians for those under 18) gave written informed consent before study participation. Controls were drawn from the same geographic location as the patients. No controls

met criteria for any current major DSM-IV-TR Axis I disorders, or had a history of psychosis, major depressive disorder (recurrent), bipolar disorder, obsessive compulsive disorder, post-traumatic stress disorder, or developmental disorders. Exclusion criteria for all participants included: sensory-motor handicaps, neurological disorders, medical illnesses that impair neurocognitive function, diagnosis of mental retardation, education less than 5th grade if <18 or less than 9th grade if ≥18, not fluent in English, DSM-IV-TR substance abuse in the past month, DSM-IV-TR substance dependence (excluding nicotine) in the past 3 months, current suicidality, history of electroconvulsive therapy (ECT) within 5-years for patients or anytime for controls, or study participation by another family member. Demographic data for the entire population are presented in [table 1](#). Separated demographic data for the recent-onset and chronic populations are presented in the [supplementary table S1](#).

For patients, clinical diagnoses were based on interviews using the Structured Clinical Interview for DSM-IV-TR (SCID), Research Version²¹ or the Kid-SCID²² for subjects <18, and information from available medical records. Recent-onset patients met DSM-IV-TR criteria for either schizophrenia, schizoaffective disorder, or schizophreniform disorder, while chronic patients met DSM-IV-TR criteria for schizophrenia or schizoaffective disorder with a duration of illness ≥5 years. Clinical symptoms were evaluated using the Scales for the Assessment of Positive Symptoms (SAPS²⁰) and Negative Symptoms (SANS²³).

Parental socioeconomic status (PSES) was evaluated using the Hollingshead 2-factor index,²⁴ premorbid intelligence was estimated using the Reading subtest from the

Wide Range Achievement Test-4 (WRAT-4),²⁵ and current intelligence was estimated from the Vocabulary and Block Design subtests of the Wechsler Abbreviated Scale of Intelligence (WASI).¹⁸ Handedness was measure by the Edinburgh Inventory.²⁶ These measures were administered by trained research assistants as part of a comprehensive neuropsychological battery.

Image Acquisition

Structural MR and diffusion MR images were acquired on a 3-Tesla whole body MRI Echospeed system General Electric scanner (GE Medical Systems) at Brigham and Women's Hospital. The 3D IR-SPGR sequence (T1) included repetition time (TR) 7.8 ms, echo time (TE) 3 ms, inversion time 600 ms, 10° flip angle, field of view (FOV) 256 mm, matrix size 256 × 256, 176 slices, and 1 mm slice thickness. Voxel size is 1 mm × 1 mm × 1 mm. The diffusion weighted images (DWI) sequence included twice refocused dual echo, echo-planar, TR 17 s, 90° flip angle, FOV 240 mm, matrix size of 144 × 144, 85 slices, 1.7 mm slice thickness, 51 gradient directions with a *b*-value of 900 s/mm², 8 nondiffusion-weighted (*b*0) images. Voxel size is 1.7 mm × 1.7 mm × 1.7 mm. During the course of the study, a software update on the scanner occurred and we included “scanner update” as a covariate in our analysis ([table 1](#)).

Image Analysis

The image analysis pipeline was separated into two processing streams, one for extracting gray matter features from structural MR images, and the other for extracting

Table 1. Demographic and Clinical Variables

	Healthy Controls Mean (SD)	Schizophrenia Patients Mean (SD)	<i>P</i> -Value
Total sample (<i>N</i>)	45	49	
Males	35	38	
Females	10	11	.978
Age (years)	33.64 (12.74)	34.43 (14.09)	.774
Education (years)	14.68 (2.27)	13.55 (2.22)	.016*
Parental socioeconomic status	2.02 (0.94)	2.38 (1.07)	.125
Premorbid IQ (WRAT-4 Reading)	108.51 (14.91)	106.54 (15.39)	.532
Current IQ (WASI)	111.71 (14.59)	102.83 (14.21)	.004*
Handedness (%)			
Right	98%	90%	
Left	0%	6%	
Mixed	2%	4%	.197
Scanner upgrade (pre/post)	29/16	21/28	.041*
Chlorpromazine equivalent	—	622.43 ± 936.67	
Age of onset of psychosis (years)	—	24.44 ± 7.76	
SANS total score	—	32.48 ± 17.23	
SAPS total score	—	26.90 ± 23.66	

Parental Socioeconomic Status - Hollingshead score (1–5 scale, 1 = highest). WRAT-4, Wide Range Achievement Test 4; WASI, Wechsler Abbreviated Scale of Intelligence—Vocabulary and Block Design subtests¹⁸; SANS, the Scale for the Assessment of Negative Symptoms¹⁹; SAPS, the Scale for the Assessment of Positive Symptoms.²⁰

*Statistically significant *P* < .05.

white matter tract dispersion from diffusion MR images. Analyses focused on three gray matter areas and 3 segments of the corpus callosum connecting them (figure 1): (1) bilateral rMGF (red); (2) bilateral STG (green); and (3) bilateral LOG (blue). All visualization of diffusion MRI data was performed in 3D Slicer (www.slicer.org) via the SlicerDMRI project (dmri.slicer.org).²⁹

Gray Matter Processing Stream

FreeSurfer Pipeline

Structural MR images were aligned to the AC-PC axis, and masked using the automated multi-atlas brain segmentation method (MABS).²⁷ Masked MR images were then processed using FreeSurfer v.5.3.²⁸ Each segmentation was visually checked by an expert rater (ECD) and manually edited when necessary to ensure optimal quality. Cortical thickness (CT), cortical curvature (Curv), and cortical surface area (SA) from all cortical vertices were extracted for each gray matter ROI (left and right rMFG; left and right STG; left and right LOG).

White Matter Processing Stream

Diffusion MRI Preprocessing

DWIs were corrected for motion artifacts, eddy-current artifacts, and EPI-distortions using in-house software (<https://github.com/pnlbwh/pnlutil>) that is described in

detail in Bouix et al.²⁹ Images were also manually masked to exclude nonbrain areas. Whole-brain 2-tensor tractography was completed for each subject³⁰ and FreeSurfer “wmparc” parcellation was nonlinearly registered to each subject’s baseline diffusion image ($b = 0$ s/mm² image). All visualization of diffusion MRI data was performed in 3D Slicer (www.slicer.org) via the SlicerDMRI project (dmri.slicer.org).³¹

White Matter Tract Extraction

We used White Matter Query Language (WMQL),³² an automated tract extraction method that uses gray matter ROIs from the FreeSurfer parcellation³³ to define white matter tracts, to extract the following tracts of interest: callosal connections of left and right rMFG; left and right STG; and left and right LOG; roughly corresponding to genu, isthmus, and splenium of the corpus callosum (figure 1).

Calculating Tract Dispersion

For each tract, we computed tract dispersion.¹² At each point along each fiber, this method measures variation of a fiber’s tangent vector in all directions orthogonal to the curve, producing a measure of local white matter dispersion. Figure 2 shows a fiber tract where warm colors indicate tract regions with high dispersion. See Savadjiev et al.¹² for further details.

MI Analysis

MI analysis was used to quantify the relationship (the dependence) between measures computed along white matter tracts and gray matter measures for each point on the cortical surface region. MI between two random

Fig. 1. The regions of interest chosen for this study: the left and right rostral middle frontal gyrus (rMGF; top); the left and right superior temporal gyrus (STG; middle); the left and right lateral occipital gyrus (LOG; bottom)

Fig. 2. Interhemispheric fiber tracts connecting the left and the right STG, shown in the left hemisphere of one of the subjects in our study. The tracts are colored by the tract dispersion (TD) measure, computed at each point along each fiber. For anatomical reference, the T1 volume is shown as background.

variables measures the amount of information they share. An MI value of 0 indicates independence. The higher the MI value, the more “dependent” the variables. We implemented this approach following the procedure described in Savadjiev et al.¹² After calculating white matter tract dispersion for each of the white matter tracts and extracting cortical gray matter features (eg, cortical thickness) using FreeSurfer, we calculated MI between tract dispersion and each of the cortical gray matter features for each tract for each subject. We first used kernel density estimation,³⁴ as implemented in the “ksdensity” Matlab function, for calculating a probability density function of the white matter feature (tract dispersion) over all white matter points, and separately the probability density function of gray matter features (CT, Curv, SA) over all cortical surface points on the FreeSurfer mesh. We calculated MI between these discretized probability density estimates using a robust numerical estimator that does not require a priori knowledge of their joint density distributions.³⁵ For additional methodological details, please refer to Savadjiev et al¹² and to Kraskov et al.³⁵

Statistical Analysis

All statistical analyses were performed in R (SAS Institute, Cary NC) and GraphPad Prism (Version 7.00a for Mac OSX, GraphPad Software, La Jolla, CA). Demographic variables were compared between groups utilizing a 2-sided *t*-test (continuous variables), a chi-square test (dichotomous variables), or a Mann–Whitney *U* test (ordinal variables). For all other statistical comparisons, age, sex, and scanner upgrade were included as covariates. All steps detailed below were run first on the entire population followed by a secondary analysis investigating the recent-onset and chronic populations separately. The purpose of this is to investigate possible influences by age and stage of illness on our results.

MI Group Comparisons

First, we conducted three omnibus MANCOVAs, one for each ROI pair: rMFG, STG, and LOG (left and right). The independent variable of interest was group, while dependent variables were (1) MI of tract dispersion and CT, (2) MI of tract dispersion and SA, and, (3) MI of tract dispersion and Curv, in left and right hemispheres. Age, sex, and scanner upgrade were included as covariates for analyses involving MI group comparisons. We chose

to employ this omnibus test to determine any significant differences existed to define the scope of our investigation and limit our susceptibility to type 1 error. If a significant main effect of group was found, post hoc ANCOVAs were performed for the six dependent variables: (1) MI of tract dispersion and CT (left and right), (2) MI of tract dispersion and SA (left and right), and (3) MI of tract dispersion and Curv (left and right). Post hoc ANCOVAs were significant if *P* < .0083 (Bonferroni-corrected).

Structural Features Group Comparisons

Although the MI analysis was main aim of this study, we conducted a similar analysis on structural variables to determine if there were group differences between individual regional features (eg, CT, tract dispersion, etc.). Again, we conducted 3 omnibus MANCOVAs for each ROI (left and right), with group as the independent variable and average values for all of the features (mean tract dispersion, mean CT, mean SA, mean Curv) as dependent variables. If a significant main effect of group was found, post hoc ANCOVAs were carried out for the 8 possible dependent variables: (1) mean tract dispersion (left and right), (2) mean CT (left and right), (3) Mean SA (left and right), and (4) mean Curv (left and right). Post hoc ANCOVAs were significant if *P* < .00625 (Bonferroni corrected).

Results

There were no significant group differences in age or sex (table 1). There was a significant difference in the proportion of individuals scanned before versus after scanner upgrade between controls and patient groups (table 1). In the schizophrenia group, the average chlorpromazine equivalent dose was 622.4 mg/kg with a range of 40 mg/kg to 5400 mg/kg and average age of onset of psychosis was 24.4 years (table 1).

MI Analysis Results

Of the 3 regional MANCOVAs, only the STG showed a significant main effect of group after controlling for age, sex, and scanner update (*F* = 2.53, *P* = .027) (table 2). None of the MANCOVAs within the recent-onset or chronic populations were significant (table 2).

Table 2. Regional MANCOVAs: Mutual Information Analysis

	Combined Population	Younger Cohort	Older Cohort
rMFG	<i>F</i> = 0.83, <i>df</i> 1 = 6, <i>df</i> 2 = 84, <i>P</i> = .546	<i>F</i> = 0.92, <i>df</i> 1 = 6, <i>df</i> 2 = 37, <i>P</i> = .491	<i>F</i> = 1.38, <i>df</i> 1 = 6, <i>df</i> 2 = 37, <i>P</i> = .246
STG	<i>F</i> = 2.53, <i>df</i> 1 = 6, <i>df</i> 2 = 84, <i>P</i> = .027*	<i>F</i> = 1.82, <i>df</i> 1 = 6, <i>df</i> 2 = 37, <i>P</i> = .121	<i>F</i> = 1.22, <i>df</i> 1 = 6, <i>df</i> 2 = 37, <i>P</i> = .316
LOG	<i>F</i> = 0.66, <i>df</i> 1 = 6, <i>df</i> 2 = 84, <i>P</i> = .684	<i>F</i> = 0.68, <i>df</i> 1 = 6, <i>df</i> 2 = 37, <i>P</i> = .664	<i>F</i> = 1.03, <i>df</i> 1 = 6, <i>df</i> 2 = 37, <i>P</i> = .424

*Statistically significant *P* < .05.

Post hoc ANCOVAs for the six MI tests in the entire sample in the STG showed a significant effect of group in the right hemispheric MI between tract dispersion and CT ($t = -2.996$, $P = .004$) and tract dispersion and SA ($t = -3.104$, $P = .003$), controlling for age, sex, and scanner update (figure 3). All remaining group comparisons of MI values did not survive correction for multiple comparisons (table 3).

Structural Features Analysis Results

Of the three regional MANCOVAs, only the rMFG showed a significant main effect of group after controlling for age, sex, and scanner update (rMFG: $f = 2.45$, $P = .019$). There were no significant group differences in the STG or LOG regions (table 4). When separated, the MANCOVAs in the STG showed trend level significance ($P = .08$) in the recent-onset population, while none of the MANCOVAs in the chronic population were significant (table 4).

Post hoc ANCOVAs for the eight features (gray and white matter) in rMFG revealed no significant group differences for any features after correction for multiple comparisons.

Correlations With Age

When we analyzed the relationship between age and MI values for SA and tract dispersion (figure 4—left panel) as well as CT and tract dispersion (figure 4—right panel) in the right STG, we show that for both the healthy controls and the schizophrenia patients the values stay relatively stable across time. In neither plot and for neither group are the correlations significantly different from zero (MI of SA and tract dispersion—SZ: $r = .03$, $P = .26$; HC: $r = -.062$, $P = .68$; MI of CT and tract dispersion—SZ: $r = .18$, $P = .20$; HC: $r = -.060$, $P = .70$).

Discussion

In this study, we observed reduced morphological dependence (as measured by MI) between CT and SA of the right STG and tract dispersion of the corresponding callosal connections in patients ($n = 49$) compared with controls ($n = 45$). MI for neither the rMFG nor the LOG and their callosal connections exhibited significant group differences. Interestingly, a group difference in the gray–white matter morphological dependence for the right STG and its callosal connections was observed despite a lack of group differences for the individual morphological measures (CT, SA, and dispersion). We also see that MI in the right STG does not exhibit a significant relationship with age in either the patient or control population.

For a more intuitive grasp of the meaning of MI changes observed in this study, one should consider that lower MI values imply greater independence between two variables (see also³⁶). For instance, in patients we observed decreased MI in right STG between white matter tract dispersion and CT (figure 3B). This suggests that the two variables in this region are less tightly coupled and less predictive of each other.

One possible interpretation of this decoupling is that in schizophrenia, the development of cortical surface morphology is less dependent on the development of the white matter geometrical structure (and vice versa). This may point to possible alterations in the biological processes that shape morphological features of white and gray matter such as axon growth, axon guidance, and myelination, on the one hand, and dendritic branching and synaptic pruning, on the other hand. Multiple genome-wide association studies have identified risk loci in schizophrenia patients that control many of these neurobiological factors (eg, Schizophrenia Working Group of the Psychiatric Genomics Consortium³⁷). More importantly, experimental evidence from primate studies show

Fig. 3. Post hoc ANCOVAs show a significant effect of group in the right hemispheric MI in the STG between tract dispersion and SA ($t = -3.104$, $P = .003$; left panel) and tract dispersion and CT ($t = -2.996$, $P = .004$; right panel) (Bonferroni-corrected threshold of $P < 0.0083$) controlling for age, sex, and scanner update.

Table 3. Post hoc ANCOVAs: Mutual Information Analysis in STG

Mutual Information of	Healthy Controls Mean (SD)	Schizophrenia Patients Mean (SD)	P-Value
Dispersion and Curv—L	2.56 (0.28)	2.61 (0.29)	.023
Dispersion and Curv—R	2.68 (0.25)	2.52 (0.27)	.014
Dispersion and SA—L	3.88 (0.27)	3.72 (0.35)	.023
Dispersion and SA—R	3.78 (0.27)	3.57 (0.36)	.003*
Dispersion and CT—L	3.65 (0.29)	3.51 (0.39)	.047
Dispersion and CT—R	3.60 (0.28)	3.37 (0.40)	.004*

*Significance at a Bonferroni-corrected threshold of $P < .0083$.

Table 4. Regional MANCOVAs: Structural Features Analysis

	Combined Population	Younger Cohort	Older Cohort
rMFG	$F = 2.45, df1 = 8, df2 = 82, P = .019^*$	$F = 1.42, df1 = 8, df2 = 35, P = .223$	$F = 1.50, df1 = 8, df2 = 35, P = .190$
STG	$F = 1.45, df1 = 8, df2 = 82, P = .188$	$F = 1.93, df1 = 8, df2 = 35, P = .086$	$F = 0.453, df1 = 8, df2 = 35, P = .880$
LOG	$F = 1.53, df1 = 8, df2 = 82, P = .169$	$F = 0.764, df1 = 8, df2 = 35, P = .635$	$F = 1.18, df1 = 8, df2 = 35, P = .339$

*Statistically significant $P < .05$.

that axonal input does exert influence over the development of cortical morphology in utero.^{38–40} In these studies, surgical removal of cortical regions can produce changes in the morphology of cortical gray matter regions that are distant from the removal site,^{38,39} suggesting a possible role for the white matter tracts connecting them. The results of this latter study lend support to our findings that gray and white matter abnormalities that are observed in adulthood could have an interrelated etiology that originated at an earlier point in development. In fact, most morphological features of the human brain are established early in development: the human brain is ~80% of adult volume by two years of age⁴¹; many white matter connections observed in adulthood are already present at birth^{41,42}; and cortical gyrification patterns are established around the third trimester, exhibiting little change after birth.^{43,44} Collectively, these studies provide evidence that the overall morphology of gray and white matter is established in early stages of development. Given this premise, variations in the relationship between gray and white matter morphology, such as those observed in this study, could be indicative of neurodevelopmental aberrations in one or both features.

This perspective is further supported by our finding that alterations in right STG MI in the SZ patients do not exhibit dramatic changes with age, despite the considerable maturational changes that are occurring in the gray and white matter during this period.^{45,46} Thus, we suggest that the morphological relationship between gray matter features and white matter tract dispersion in the STG is already abnormal at illness onset and subsequently does not experience a large amount of deterioration with disease progression or increasing age.

Our findings of diminished gray/white matter morphological dependence within the STG and its callosal connections are supported by considerable evidence from multiple studies that suggest that neurodevelopmental abnormalities exist in these regions in schizophrenia patients.^{47–52} Aberrations in gray matter volume in the STG, as well as white matter diffusivity measures (namely FA) in the corpus callosum, have been found in first-episode and chronic patients.^{4,53,54} Similarly, structural alterations have also been reported in subjects exhibiting prodromal symptoms, and in unaffected first-degree relatives, indicating a possible genetically mediated feature present before illness onset.^{47–52} We were surprised to find no significant differences in MI for the relationship between the rMFG and the genu, as frontal areas have also been implicated in an array of studies in schizophrenia patients,^{55–57} and our earlier studies have previously indicated sexually dimorphic dispersion differences within the genu in an early course schizophrenia population.^{13,14}

The present study does have limitations. First, the CIDAR study collected patients diagnosed with schizophrenia who were at different stages of the disease, ie, chronic schizophrenia and recent-onset schizophrenia patients. Although we controlled for age in the analyses, it is possible that the range of ages could have influenced our results. Second, although all study participants were scanned on the same scanner, a software update occurred during the course of this study. To account for possible differences introduced by using 2 different software versions, we included “scanner update” as a covariate in the statistical analyses. Finally, underlying biological explanations of the observed reduction in morphological

Fig. 4. Correlations between age and the right hemispheric MI in the STG between tract dispersion and SA (left panel) and tract dispersion and CT (right panel) for both schizophrenia patients (red squares) and controls (blue circles). The correlation coefficients and P -values for each group are as follows: MI of SA and tract dispersion—schizophrenia (red squares—left panel): $r = .03$, $P = .26$; healthy controls (blue circles—left panel): $r = -.062$, $P = .68$. MI of CT and tract dispersion—schizophrenia: $r = .18$, $P = .20$ (red squares—left panel); healthy controls: $r = -.060$, $P = .70$ (blue circles—right panel).

dependence cannot be easily untangled with the present method, and therefore, our interpretations are preliminary, necessitating further studies and replication in a larger sample. Accordingly, our intent is for this study to be considered hypothesis-generating. Despite this limitation, we believe that the present work demonstrates the importance of not only studying neuroimaging features as independent entities, but also how they are associated with each other.

In summary, our study demonstrates there is reduced morphological dependence between gray and white matter in the STG and associated callosal connections in schizophrenia patients that may arise due to aberrant neurodevelopmental processes. Future studies in larger cohorts are needed to determine the extent of related gray and white matter neurodevelopmental structural pathologies in the brain in schizophrenia patients. MI analyses of gray and white matter in both genetic- and clinical high-risk populations will be of critical importance, as it will provide further support for the neurodevelopmental hypothesis. We are also very interested to investigate whether MI is influenced by other characteristics of the sample, such as sex, as it can help us further our understanding of both the nature of the morphological relationship between the two and how it may contribute to schizophrenia pathophysiology.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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