# Sex, Age, Symptoms and Illness Duration and Their Relation with Gyrification Index in Schizophrenia

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## Abstract

**Introduction:** The Gyrification Index (GI) represents the degree of cortical folding and is of special interest in schizophrenia, since alterations in cortical folding indirectly reflect white matter development and axonal connectivity underneath. To the best of our knowledge, very few studies have investigated the effect of sex on GI in schizophrenia. Differences in the GI between patients with schizophrenia and healthy controls and the relation between sex, age symptoms and duration of illness with GI were investigated. **Methods:** T1-images were acquired from schizophrenia patients (24 males [SZ-M] and 24 females [SZ-F]) and healthy volunteers (24 males [NC-M] and 24 females [NC-F]) matched for age, sex and handedness. GI analyses were performed using the fully automated CIVET pipeline. **Results:** Significantly lower GI was found in patients relative to controls bilaterally in frontal, temporal, and parietal cortex. Sex differences were found: negative correlation was found between the duration of illness and the right parietal GI and right occipital GI in SZ-M, while SZ-F was found in the left frontal and bilateral temporal GI. Patients, regardless of sex, showed positive correlations between negative symptoms and GI in the right occipital. NC-F had greater GI values than SZ-F and both male groups. **Conclusions:** Since GI reflects, in part, alterations in cerebral development and connectivity, the decrease in GI observed in patients is in agreement with the neurodevelopmental model of disconnectivity in schizophrenia; in addition, we emphasize the importance of sex differences in schizophrenia.

**Key Words:** Schizophrenia, Sex Differences, Magnetic Resonance Imaging, Gyrification Index, Illness Duration, Age, Symptoms

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## Introduction

The last couple of decades have witnessed a boom in the development of sophisticated methods of investigating brain structure and function, but a great deal of work still lies ahead in order to unravel the neurobiological mechanisms underlying schizophrenia (1-4). Numerous brain regions have been implicated in the pathophysiology of this genetically and behaviorally complex disorder, suggesting that schizophrenia is not caused by any focal brain abnormality, but results from disturbed interactions between brain regions. In this regard, Friston and Frith (1995) (5) have advanced that the core pathology of schizophrenia is an impaired neuromodulation of synaptic plasticity, leading to abnormal functional integration of neural systems. One way to assess this theory is to measure cortical folding, which reflects cortico–cortical connectivity, in addition to the intracortical organization (6). This cortical folding is measured through the Gyrification Index (GI).

The Gyrification Index (GI) represents the degree of cortical folding by calculating the ratio of the entire inner cortical contour of the brain to that of the exposed outer surface contour. An increase in the GI index is thus correlated

to an increase in the number and complexity of gyri (7). In 1991, Armstrong et al. (8) stated that change in this gyrification reflects aspects of the morphological development of the cortical layer. Developmentally, gyrification takes place following the completion of neuronal migration during the gestation period (9). The greatest increase in GI values occurs between 22 and 42 weeks of gestation (10). The Gyrification Index stabilizes shortly after birth and appears to be stable thereafter, even in the presence of atrophic processes affecting gray and white matter at a later age (10).

The Gyrification Index is of special interest in schizophrenia, since alterations in cortical folding indirectly reflect white matter development and axonal connectivity underneath (10, 11). Results of gyral folding (using GI) in healthy population derive mainly from postmortem studies (7, 10, 12). For example, Zilles et al. (1988) (7) measured the GI bilaterally in the brains of 25 males and 36 females without apparent neurological diseases. The GI was greatest in the prefrontal and parieto-temporal cortex, and no significant sex differences in the GI were observed.

Very few studies have attempted to investigate GI in schizophrenia patients (13-16) and those that did focused mainly on the frontal lobe. These studies reported both greater (15, 17) and lower gyral complexity (18, 19). A study by Sallet et al. (2003) (20) and Palaniyappan et al. (2011) (16) reported global reductions, but with fluctuating regional increases in right anterior prefrontal cortex and bilateral frontomarginal regions. Harris et al. (2004) (15) compared a larger sample (n=34) of first-episode patients to healthy controls (n=36) and assessed the prefrontal, temporal, parietal, and occipital lobes. The authors found a trend toward reduction in the left prefrontal region but significant increases were observed in the right temporal regions. These structural abnormalities may provide insight into differences in schizophrenia symptomatology (14, 20, 21).

Very few studies have investigated the effect of sex on GI measures in schizophrenia (20, 22, 23). Only the study by Vogeley et al. (2000) (23) found an effect of sex and diagnosis on the degree of gyral folding. Vogeley et al. conducted the study on postmortem brains of patients with schizophrenia (n=24) and healthy controls (n=24) using gyrification measures, specifically in the prefrontal region. The authors found a significant effect of diagnosis-by-sex interaction on the GI in the right prefrontal, where male patients had higher GI in comparison to healthy men, while no significant difference was observed in the female groups. A second study by Highley et al. (2003) (22) performed gyrification measures on frontal, temporal, parietal and occipital regions in 61 (21 female) patients with schizophrenia in comparison with 42 healthy controls (21 females). The authors found no effect of diagnosis or sex on the degree of folding.

Harris et al. (2007) (19) used an automated gyrification measure in the frontal lobe to compare between schizophrenia patients (14 males and 11 females) and patients with mental retardation and healthy controls. Schizophrenia patients had reduced gyrification; however, the authors report no significant effect of sex on Gyrification Index. Similarly, Cachia et al. (2008) (21) investigated local sulcal index in schizophrenia patients (10 females and 20 males) with hallucination in comparison with healthy controls. Reductions were significant in the superior temporal sulcus bilaterally in the left middle frontal sulcus, with no significant main effect of sex on the results.

More recently, Palaniyappan et al. (2012) (24) performed gyrification analyses in a group of 57 schizophrenia patients (50 males), and a second time after exclusion of the 7 female subjects; the authors report reductions in left insula, the superior temporal gyrus, caudal superior temporal and inferior parietal regions. However, the exclusion of the female subjects did not change the results. The authors recommended caution in the interpretation of these results and pointed out that studies with equal male/female ratios are needed.

The aim of the present study was threefold: 1) to investigate differences in the GI between patients with schizophrenia and healthy controls; 2) to investigate the main effects of sex on the GI in larger samples of patients; and, 3) to investigate the main effects of age and duration of illness on the GI. Based on previous studies, we hypothesized that: 1) patients will have lower GI than healthy controls; 2) female patients will show less deficit than male patients relative to the same-sex controls (this hypothesis is based on several reports of more structural brain abnormalities in males than in females with schizophrenia diagnosis (25-30); 3) the GI will show deterioration with age, which will be more pronounced in schizophrenia patients; and, 4) in addition, the duration of illness will be associated with lower GI.

## Methods

### *Participants*

A total of 96 subjects were included in the present study. Inclusion criteria for the schizophrenia group were a *DSM-IV* (31) diagnosis of schizophrenia with no medical or neurological diseases and no concomitant Axis-I or Axis-II disorders. Forty-eight schizophrenia patients (24 males [SZ-M] and 24 females [SZ-F]) and 48 healthy volunteers (24 males [NC-M] and 24 females [NC-F]) participated in the study after signing a detailed informed consent approved by the local scientific and ethics committees.

Schizophrenia patients and healthy controls were matched for age, sex, and handedness (32). SZ-M:

**Table 1 Clinical Assessments in Schizophrenia Patients**

| | Men Mean (SD) | Range | Women Mean (SD) | Range | P Value |
|---|---|---|---|---|---|
| Age (years) | 31.25 (7.96) | 20–49 | 33.04 (8.38) | 21–51 | 0.452 |
| Duration of illness (years) | 11.04 (10.63) | 2–25 | 8.04 (7.55) | 1–27 | 0.265 |
| Age of onset (years) | 21.47 (4.78) | 14–35 | 25.83 (7.37) | 18–48 | 0.021 |
| PANSS positive score | 17.083 (5.76) | 8–29 | 19.62 (7.49) | 9–34 | 0.194 |
| PANSS negative score | 16.12 (4.45) | 10–26 | 20.79 (7.69) | 9–39 | **0.038** |
| PANSS general score | 36.96 (7.11) | 25–54 | 42.41 (12.66) | 24–72 | 0.072 |
| PANSS total score | 70.92 (13.92) | 46–107 | 82.83 (26.08) | 41–140 | **0.05** |
| Chlorpromazine equivalence (mg/day) | 542.29 (372.09) | 100–1,500 | 438.71 (276.35) | 66–1,100 | 0.279 |

mean=31.25 years, SD=7.97; NC-M: mean 33.50 years, SD=8.69, p=.355; SZ-F: mean=33.04 years, SD=8.38; NC-F: mean=29.92 years, SD=7.15, p=.171. No significant differences between groups were found in the parental socio-educational status (SZ-M: mean=2.82, SD=0.61; NC-M: mean=2.32, SD=1.12; SZ-F: mean=2.63, SD=1.06; NC-F: mean=2.18, SD=1.13, p=.183) as assessed by the National Occupational Classification (NOC) (33) on a scale ranging from 1 to 4. There were no significant differences between male and female patients in either mean duration of illness or dose of antipsychotic medication in chlorpromazine equivalence. Patients were stabilized on one or more atypical antipsychotic. The effects of antipsychotic medications on GI were considered through estimation of chlorpromazine dose equivalents (34). Patients with *DSM-IV* (31) criteria of affective, schizoaffective and schizophreniform psychosis were excluded from the study. Patients with past or present neurological or Axis-I psychiatric disorder, alcoholism or drug abuse were also excluded. Control participants were screened with the non-patients edition of the Clinical Interview for DSM-IV (SCID) (35). Symptoms severity was rated according to the Positive and Negative Syndrome Scale (PANSS) (36). Handedness was evaluated with the Edinburgh Inventory (32) (see Table 1). Illness onset was defined as the date of "first consultation" at the hospital.

## Magnetic Resonance Imaging Acquisition

Individual high-resolution co-planar anatomical images were acquired (three-dimensional, spoiled gradient echo sequence; slices=176, slice thickness=0.98 mm, TR=19 ms, TE=4.92 ms, flip angle=25°, matrix 256 x 256 voxels) on an MRI Siemens TRIO system at 3.0 Tesla, which is operational at the University of Montreal Geriatric Institute.

## Magnetic Resonance Imaging Analysis

### Gyrification Index Preprocessing

Gyrification index analyses were done using the fully automated CIVET pipeline, which consists of 18 steps. For details please see references (37-42) and the following link: http://www.nitrc.org/plugins/mwiki/index.php/neurobureau:CIVETPipeline.

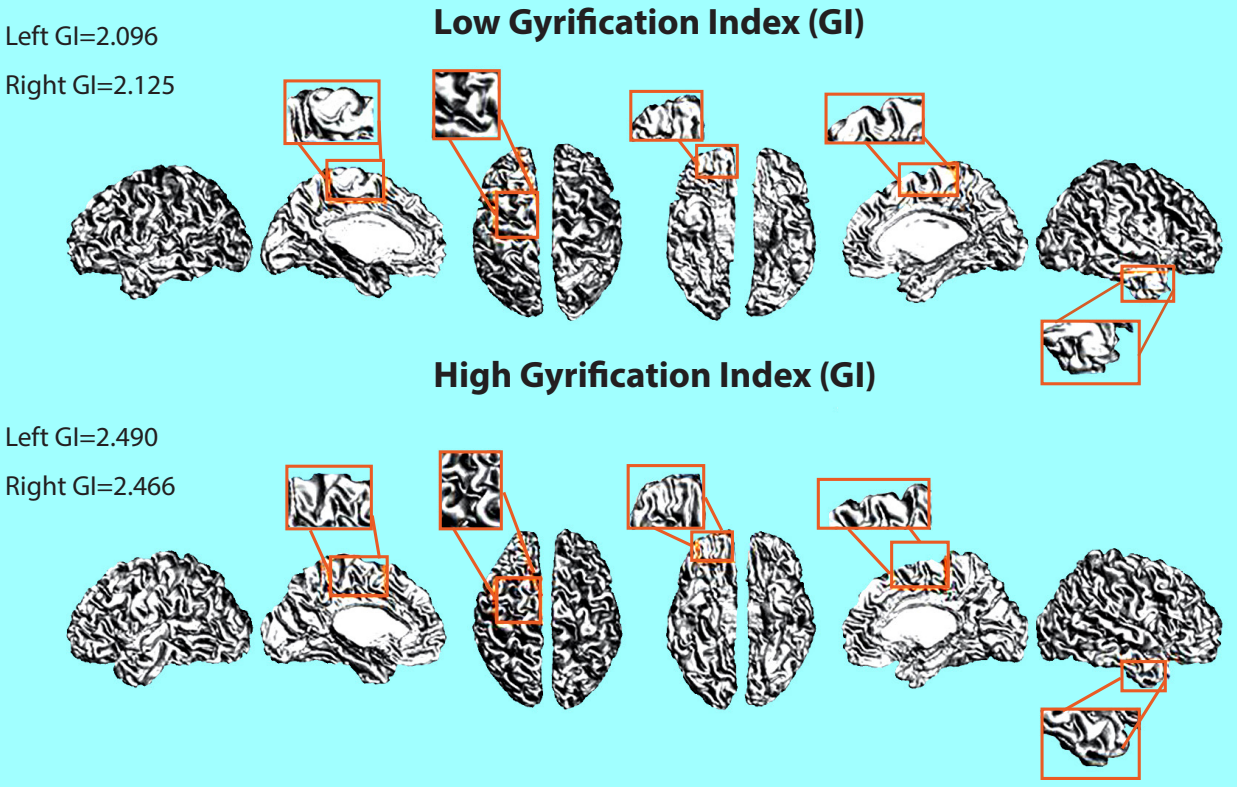
### Gyrification Index Measurement

An intermediate cortical surface, halfway between the inner and outer CLASP (Constrained Laplacian Anatomic Segmentation using Proximity) surfaces, was used for measuring the surface morphometrics, as it represents a relatively unbiased representation of both sulcal and gyral regions (43). The cortical area was calculated in the whole hemisphere and each lobar region by summing the Voronoi area based on geodesic distances over the folded topology of the surface (44). The middle cortical surface was divided into the sulcal and gyral regions by thresholding the depth map (i.e., 3D Euclidean distance from each vertex to the nearest voxel on the convex hull volume (45). The threshold of the depth map was determined from the fact that the human cerebral cortex is a highly folded sheet with 60–70% of its surface area buried within folds (7, 46). The mean GI was defined as the ratio between the total surface area and the superficially exposed surface areas such as the gyral regions in each hemisphere and lobe (7). Please see Figure 1 as an example.

## Statistical Methods and Analysis

We used the unified statistical approach to deformation-based morphometry applied to the cortical surface (47), which is specifically performed when using age and gender as covariates. The cerebral cortex has the topology

**Figure 1** Example of High and Low Gyrification Index

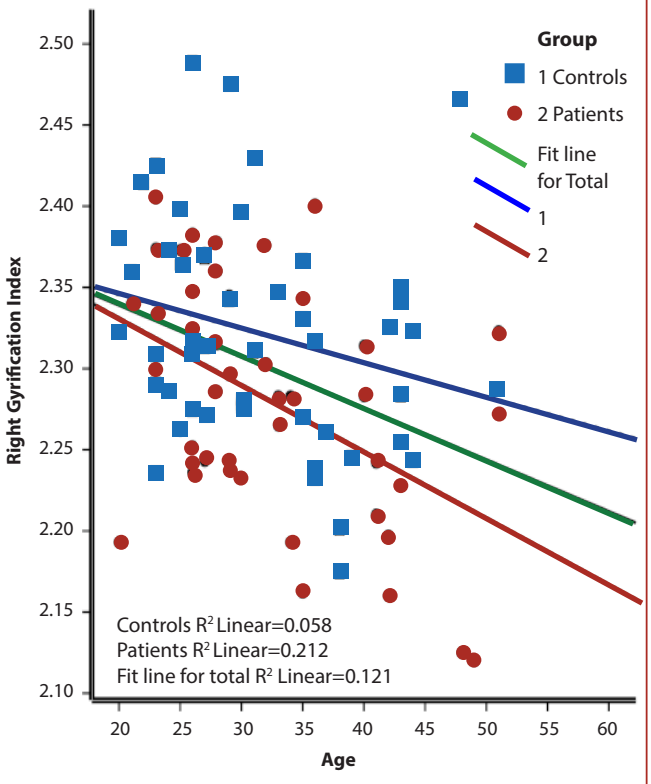



of a 2D highly convoluted sheet. As the brain develops over time, the cortical surface area, thickness, curvature, and total GM volume change. It is highly likely that such age-related surface changes are not uniform. By measuring how such surface metrics change over time, the regions of the most rapid structural changes can be localized. We avoided using surface flattening, which distorts the inherent geometry of the cortex in our analysis and is only used in visualization. To increase the signal-to-noise ratio (SNR), diffusion smoothing—which generalizes Gaussian kernel smoothing to an arbitrary curved cortical surface—has been developed and applied to surface data (2D smoothing). As an illustration, our group has demonstrated how this new surface-based morphometry can be applied in localizing the cortical regions of the gray matter tissue growth and loss in the brain images longitudinally collected in a group of children and adolescents. Further studies (48, 49) stated that each of the segmentation, thickness computation, and surface registration procedures are expected to introduce noise in the thickness measure. To counteract this, data smoothing was used to increase the signal-to-noise ratio (SNR) and the sensitivity of statistical analysis. For analyzing data in 3D whole brain images, Gaussian kernel smoothing is widely used, which weights neighboring observations according to their 3D Euclidean distance.

In the present study, however, the data lie on a 2D surface so the smoothing must be weighted according to distance along the surface. This method is adopted to reduce the noise in the thickness measure, especially when covarying with age and gender. Diffusion smoothing, that smooths data on an explicit 2D cortical surface representation, is based on the observation that, in Euclidean space, Gaussian kernel smoothing is equivalent to solving an isotropic diffusion equation. This diffusion equation can also be used on the surface manifold to increase the SNR. This is done to reduce noise and to overcome problems caused by neuroanatomic variability within the gender and age groups. In addition, mixed-model regression, which accounts for missing data, irregular intervals between measurements, and within-person correlation, was used to examine the developmental trajectories (50). The threshold for statistical significance was set at an $\alpha$ of 0.05. Correction for multiple comparisons was needed to control the false-positive rate. All statistical thresholds were determined by application of the false discovery rate (FDR) technique controlling procedure for multiple comparisons. This approach is reported to be effective for the analysis of neuroimaging data (51).

A factor analysis (or "diagnostic group") diagnosis-x-gender was performed for variables revealing significance for the GI. Then analysis of covariance (ANCOVA), with mean

**Figure 2A Representing Group x Age Interaction in the Right Hemisphere**




GI as the dependent variable with separate analyses for the left and right hemispheric, in addition to each lobe GI, was performed according to a general linear model corrected for multiple comparisons. A series of univariate ANOVAs were subsequently performed according to the general linear model. Regression analyses were also performed, using GI as the dependent variable and age, symptomatology and duration of illness as regressors. Potential interactions between regressors and diagnosis and sex were tested. Analyses were performed using the SPSS 17 software. Type I error was controlled by adopting Bonferroni corrections at $p<0.05$.

## Results

### *Psychiatric Assessments*

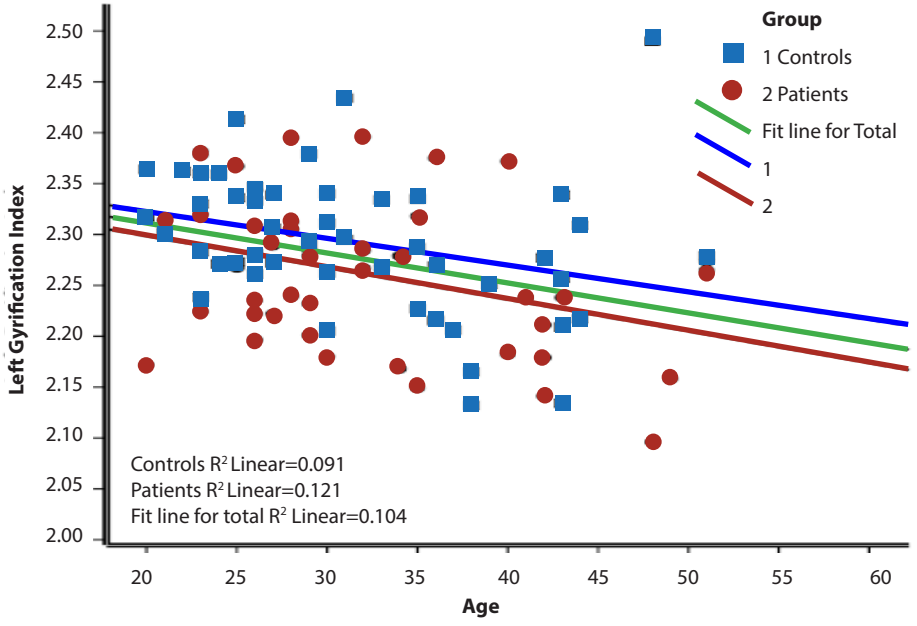
T-test analyses showed a significant difference in negative and total PANSS scores and age of onset between males and females with schizophrenia, but no differences were found in medication or illness duration (see Table 1).

### *Gyrification Index*

#### Results by Hemisphere

The independent sample t-test showed a significant main effect of group on the right hemisphere GI (t=2.723, p=.008) and left hemisphere GI (t=2.127, p=.037), such that the patient group exhibited lower GI compared to the

**Figure 2B Representing Group x Age Interaction in the Left Hemisphere**




Figures 2A and 2B show more rapid decrease in GI bilaterally with progressive age in the patient group compared to controls. **(A)** represents Group-by-Age interaction in the right hemisphere regression GI ($r^2$=.121, β=-.347, t=-3.592, p=.001); **(B)** represents Group-by-Age interaction in the left hemisphere GI ($r^2$=.104, β=-.323, t=-3.311, p=.001).

**Figure 3A Representing Age x Sex Interaction in the Right Hemisphere**

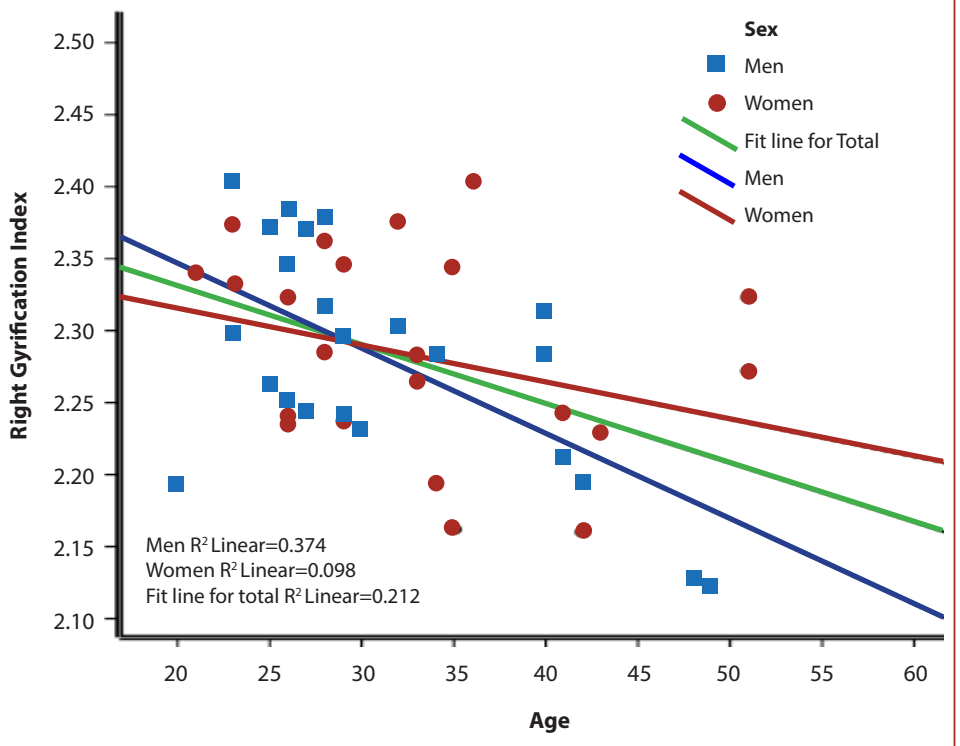
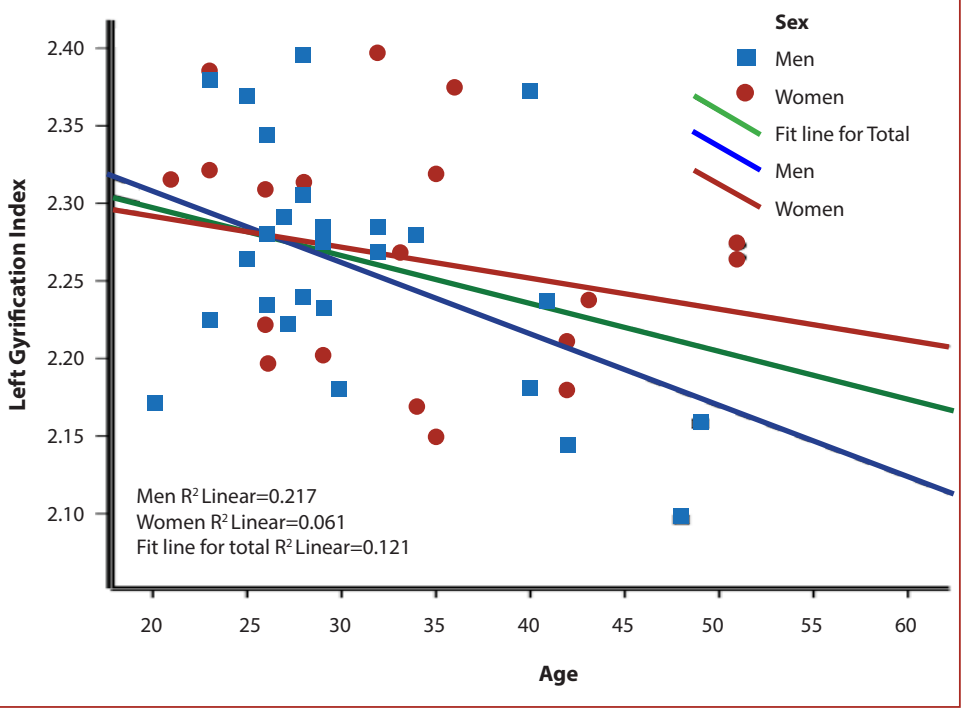



**Figure 3B Representing Age x Sex Interaction in the Left Hemisphere**




Figures 3A and 3B show that males with schizophrenia had greater GI reductions bilaterally, yet more pronounced in the right hemisphere with progressive age compared to females with schizophrenia. **(A)** represents Age x Sex interaction on the right hemisphere GI ($r^2$=.212, β=-.461, t=-3.523, p=.001); **(B)** represents Age x Sex interaction in the left hemisphere GI ($r^2$=.121, β=-.348, t=-2.514, p=.016).

control group. Based on previous findings, second-level ANOVA was performed on the female and male groups separately. There was a significant main effect of group in males on the right hemisphere GI (t=2.545, p=.018), and only a trend on the left hemisphere GI (t=1.947, p=.058), where SZ-M showed a significantly lower GI compared to control males. No main effect of group was observed in females.

## Regression and General Linear Model Analyses with Hemispheres

General linear model revealed a Group-by-Age interaction in the GI of the right (F[1,95]=2.221, p=0.019) and left hemisphere (F[1,95]=2.239, p=0.018), such that the diagnosis of schizophrenia affected the rate of GI lost with age. The direction of this interaction was such that increased age correlated with lower GI in the right hemisphere and in the left hemisphere GI (see Figure 2A and 2B), with more rapid decrease in GI bilaterally with progressive age in the patient group compared to controls.

The examination of patients revealed an Age x Sex interaction in the right and left hemisphere GI, showing that males with schizophrenia had greater GI reductions bilaterally, yet more pronounced in the right hemisphere with progressive age compared to females with schizophrenia (see Figure 3A and 3B). Furthermore, an interaction was observed between duration of illness and sex ($r^2$=.244, β=-.494, t=-3.856, p=.0001), demonstrating a greater decrease in GI in the right hemisphere with the duration of illness only in males with schizophrenia. There were no significant correlations found between hemispheric GI and symptoms in either group or patients.

**Table 2 Lobar Gyrification Index Measures**

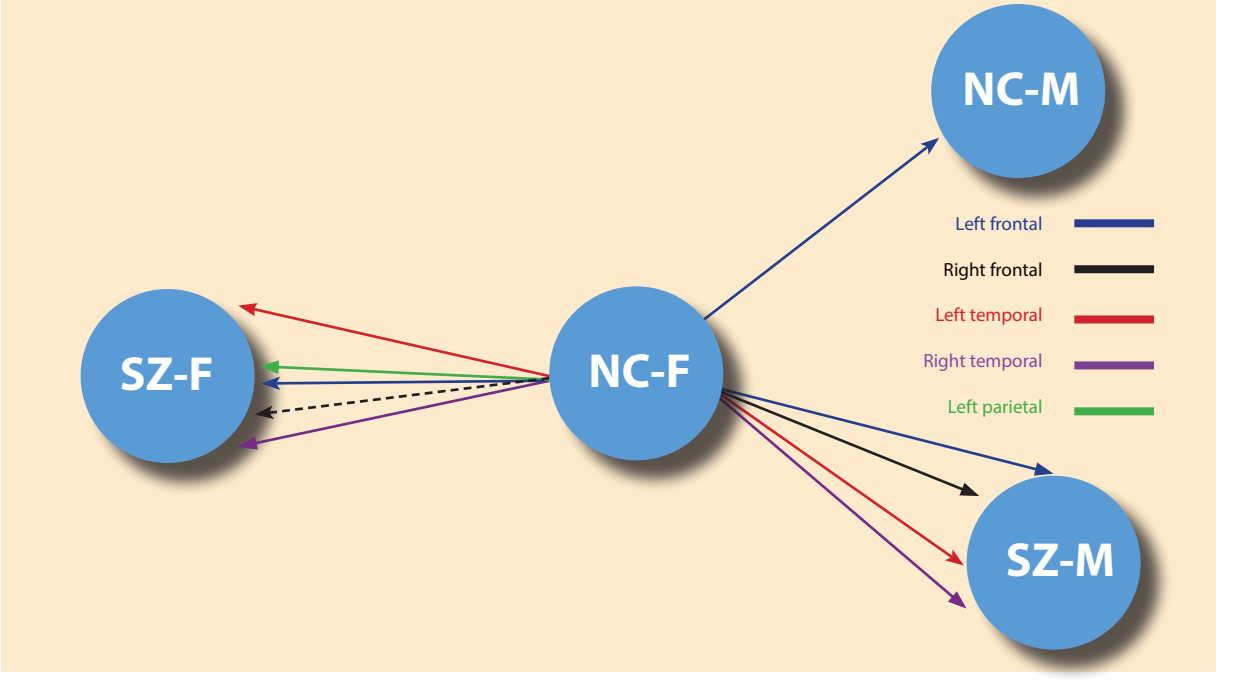
| | NC-M Mean (SD) | NC-F Mean (SD) | SZ-M Mean (SD) | SZ-F Mean (SD) |
|---|---|---|---|---|
| **Left** | | | | |
| Frontal | 2.4366 (0.1137) | 2.5341 (0.1060) | 2.3904 (0.1302) | 2.4139 (0.1181) |
| Temporal | 2.7597 (0.1817) | 2.8517 (0.1777) | 2.7055 (0.1782) | 2.6929 (0.1769) |
| Parietal | 3.0085 (0.1717) | 3.090 (0.1813) | 2.9730 (0.1795) | 2.9463 (0.1373) |
| Occipital | 2.0797 (0.1578) | 2.117 (0.1702) | 2.0565 (0.1511) | 2.1097 (0.1607) |
| **Right** | | | | |
| Frontal | 2.4473 (0.1261) | 2.5287 (0.0978) | 2.3986 (0.1135) | 2.4355 (0.1324) |
| Temporal | 2.6461 (0.1639) | 2.7402 (0.1581) | 2.5912 (0.1372) | 2.5525 (0.1758) |
| Parietal | 3.0525 (0.1375) | 3.100 (0.1408) | 3.0095 (0.1437) | 3.0081 (0.1793) |
| Occipital | 2.2532 (0.1317) | 2.3101 (0.1525) | 2.1942 (0.1393) | 2.2556 (0.1513) |

NC-M=healthy male volunteers; NC-F=healthy female volunteers; SZ-M=male schizophrenia patients; SZ-F=female schizophrenia patients.

## Results by Lobe

The independent sample t-test between patients and controls showed significant differences in the left frontal

**Figure 4 Represents Higher GI in Female Controls in Comparison to Male Controls and Both Groups of Patients**



lobe GI (t=3.358, p=.001), left temporal (t=2.902, p=0.005) and left parietal GI (t=2.596, p=0.011), the right frontal lobe GI (t=2.886, p=0.005), the right temporal lobe GI (t=3.672, p=0.001) and right parietal lobe GI (t=2.198, p=0.030), such that the patient group exhibited lower GI compared to the control group. ANOVA was performed for the 4 groups: NC-M, SZ-M, NC-F and SZ-F. Differences between groups were significant in the left frontal ($F[1,95]=6.949$, $p=0.001$) where NC-F had higher GI than NC-M ($p=0.030$), SZ-M ($p=0.001$) and SZ-F ($p=0.004$); in the left temporal ($F[1,95]=3.924$, $p=0.011$) where NC-F had higher GI than SZ-M ($p=0.034$) and SZ-F ($p=0.016$); in the left parietal ($F[1,95]=0.021$, $p=0.023$) where NC-F had higher GI than SZ-F ($p=0.023$); in the right frontal ($F[1,95]=5.165$, $p=0.002$) where NC-F had higher GI compared to SZ-M ($p=0.001$) and SZ-F ($p=0.046$); in the right temporal ($F[1,95]=6.263$, $p=0.001$) where NC-F showed higher GI than SZ-M ($p=0.01$) and SZ-F ($p=0.001$) (see Figure 4).

### Regression Analyses with Lobes

Regression analyses revealed a negative correlation between the duration of illness and the right parietal GI ($r^2=0.166$, $\beta=-0.407$, $t=-2.092$, $p=0.048$) and right occipital GI ($r^2=0.183$, $\beta=-0.427$, $t=-2.218$, $p=0.037$), such that male patients show more rapid decrease in GI. Women showed more rapid decrease in the left frontal GI ($r^2=0.306$, $\beta=-0.553$, $t=-3.115$, $p=0.005$), left temporal GI ($r^2=0.211$, $\beta=-0.459$, $t=-2.422$, $p=0.024$) and right temporal GI ($r^2=0.280$, $\beta=-0.529$, $t=-2.927$, $p=0.008$).

Regression analyses between symptoms and GI performed in patients regardless of sex showed positive correlation between negative symptoms and the right occipital GI ($r^2=0.170$, $\beta=0.398$, $t=3.064$, $p=0.004$). SZ-M showed negative correlations in the left occipital GI with negative symptoms ($r^2=0.221$, $\beta=-0.470$, $t=-2.495$, $p=0.021$), while SZ-F showed positive correlations between negative symptoms and the right occipital GI ($r^2=0.230$, $\beta=0.479$, $t=2.561$, $p=0.018$).

## Discussion

The main findings of the present study are:

1) significant lower values of the overall GI and in individual lobes in schizophrenia relative to normal controls;

2) significant lower values of the GI in the right hemisphere in schizophrenia males relative to the same-sex controls (no difference between female groups);

3) GI values decrease with age in healthy controls (with no sex difference) and in patients (greater in males than in females), with a more progressive deterioration in the right hemisphere in schizophrenia;

4) significant GI values decrease with the duration of illness in schizophrenia males but not in schizophrenia females;

5) patients showed significantly lower GI in bilateral frontal, bilateral temporal, and bilateral parietal compared to controls;

6) female controls had greater GI values than schizophrenia females and both male groups in the left frontal; greater values than both patient groups in the bilateral temporal and right frontal; and greater values in the left parietal compared to females with schizophrenia;

7) negative correlation was found between the duration of illness and the right parietal GI and right occipital GI in male patients;

8) female patients had a negative correlation between the duration of illness and the left frontal and bilateral temporal GI;

9) in all patients, positive correlations were found between negative symptoms and GI in the right occipital;

10) male patients showed negative correlations in the left occipital GI with negative symptoms; and,

11) female patients showed positive correlations between negative symptoms and the right occipital GI.

These findings point to abnormalities in the morphological development of the cortical layer in schizophrenia. These alternations were generalized bilaterally in the frontal, temporal and parietal cortex, and in concordance with previous structural findings in the literature (21, 52, 53). Taking into consideration two facts—1) GI values reach their maximum during the first years of life and decrease gradually during childhood and 2) the gyrification pattern is mostly completed at birth, yet the sulco-gyral folds continue to develop until early adulthood (10)—we advance that neurodevelopmental brain changes may be present at the onset of the illness (25, 30, 54-59), with further changes occurring during progression of schizophrenia (54, 60-63), specifically in males (54, 64). The finding of sex difference in the GI in schizophrenia is consistent with several reports of more neuroanatomical abnormalities in males relative to female patients. For example, Narr et al. (2001) (65) found a Sex-by-Diagnosis interaction with schizophrenia males showing a greater loss of superior temporal sulcal slope asymmetry in the right hemisphere than schizophrenia females. In addition, the authors found greater variability in the longitudinal fissure, reflecting both larger sulci and larger cerebrospinal fluid space in males relative to female patients. In a different study, Bullmore et al. (1995) (28) showed a global reduction in the right hemisphere radius of gyrification in males but not in females with schizophrenia. Similar structural sex differences have been found in volumetric and cortical thickness studies (25-27, 29, 30).

In addition to sex difference in the GI in schizophrenia, we have found a significant decrease in GI values with the duration of illness. Decreases were seen in the right parietal

and right occipital lobes in men. Women patients, on the other hand, showed decreases mostly in the left hemisphere (left frontal and temporal, and right temporal). Indeed, several studies have shown a progressive decrease in global brain measurements associated with illness duration (66, 67), specifically in frontal (68, 69) and temporal lobes (66, 68); however, the present study is, to the best of our knowledge, the first report of sex differences in GI taking into consideration the duration of illness.

The overt clinical expression of some psychiatric and neurodevelopmental disorders may be a reflection of an underlying abnormality in growth of cortical convolutions (70). Hence, it is plausible that the significant decrease in the GI observed in schizophrenia is related to the disease itself. Nevertheless, we found only an association between occipital GI and negative symptoms; in addition there was sex difference where female patients with more negative symptoms also had greater GI in the right occipital cortex, and male patients who had greater negative symptoms had lower GI in the left occipital cortex. A study by Onitsuka et al. (2007) (71) showed a relation between reduced volumes in the visual association areas and hallucinations. Their study included only male schizophrenia patients. Bijanki et al. (2015) (72) reported an association between increased white matter fractional anisotropy in the occipital lobe and increased score on the Scale for the Assessment of Negative Symptoms (SANS) in schizophrenia patients. The authors did not report any sex differences. Of relevance is a study by Mitelman et al. (2003) (73) showing that patients with negative symptoms and poorer outcome had significantly lower gray matter volumes in the temporal and occipital lobes compared to better outcome patients and healthy controls.

At this point, it is of important relevance to note that abnormalities in GI in our group of schizophrenia patients in comparison to healthy controls were not the same regions that correlated with schizophrenia clinical symptoms as measured by the PANSS. We postulate that cognitive deficits play a role in such discrepancy. Several studies have shown abnormalities in these regions in relation with deficits in mental rotation abilities (74), IQ performance (75), language processing (76), and face recognition (77).

Along this line of evidence, Jou et al. (2005) (78) demonstrated abnormalities in cortical gyrification in individuals at increased genetic risk of schizophrenia (i.e., not presenting the full schizophrenia symptomatology).

Interestingly, female controls had greater GI values than schizophrenia females and both male groups in the left frontal; greater values than both patient groups in the bilateral temporal and right frontal; and, greater values in the left parietal compared to females with schizophrenia. Similar findings were reported by Luders et al. (2006) (79). In this study, the authors found increased gyrification in frontal, parietal, temporal, and occipital regions in healthy females compared to healthy males.

While previous findings investigating GI in schizophrenia (20, 22, 23) did not find any significant sex difference in our study, decreased GI was observed in different regions in schizophrenia males relative to control males, and in females with schizophrenia compared to control females. Furthermore, sex differences were observed in regions showing lower GI in association of age as well as illness duration, which in itself suggests a differential neuropathological process implicated in male and female patients. Palaniyappan et al. (2011) (24) showed a strong negative correlation between age and Gyrification Index in schizophrenia in general without reference to sex, suggesting a higher degree of age-related morphometric changes in patients. However, to our knowledge, this is the first study to report such sex differences in relation to age and duration of illness.

Several elegant hypotheses have been proposed to explain sex differences in the schizophrenia brain. On one hand, Crow et al. (2008) (80) suggested that sex differences related to psychosis are attributed to a genetic species-specific variation related to a locus on the X and Y chromosomes. Gene expression in this region is influenced by the degree of X and Y chromosomes pairing in male meiosis—a process referred to as "MSUC" (meiotic suppression of unpaired chromosomes), which normally would lead to a more rapid mean rate of lateralization in females than in males (this in turn relates to the higher incidence rate of language delays and dyslexias in males). This complex theory posits that language disturbances are integral to psychosis. Lateralization or cerebral torque (where the right frontal lobe is larger than the left, while the left occipito-temporo-parietal is larger than the right) is due to the development of neural connections associated with language: from right to left in relation to motor speech output and from left to right in relation to speech perception. Disturbance in this neural development was proposed as the basis of the genetic predisposition to psychosis (i.e., the authors suggest that schizophrenia is a result of an abnormal cerebral lateralization associated with the emergence of language in humans). When this hypothesis is considered in the context of brain structures, it may explain the higher levels of anomalies found in males compared to female patients in our study and the differences in the development of schizophrenia in males and females in general (81).

On the other hand, the influence of sex steroid hormones has also been considered (82, 83). These studies strongly suggest that the neuroprotective effects of estrogen (which influences sexual characteristics, development of the brain aminergic networks, and the ability to adapt to stressful events) enhance the vulnerability threshold for psychosis by the dopamine downward regulation. Such mechanism

may explain the later onset and the more positive course of female schizophrenia. In this vein, an amalgam of research has been proposed to explain the presence of significant brain structure abnormalities in schizophrenia males in comparison to normal control males and schizophrenia females, such as greater enlargement of the lateral and third ventricles and decreased frontal and temporal lobe volumes (84, 85) and disease progression (86-88). With regards to the latter, Riecher-Rossler et al. (1994) (89, 90) and Hafner (2003) (87) found that increased levels of estrogen in females with schizophrenia with normal menstrual cycles were significantly associated with lower schizophrenia symptoms, suggesting that estrogen had "a weak neuroleptic-like effect on schizophrenia symptoms."

Because cortical gyrification is an important marker of cerebral development (10), we investigated the relationship between GI and age in our 96 subjects. We found a more pronounced decrease in GI with age in schizophrenia patients relative to healthy controls. Cortical convolution is influenced by the degree of thalamo-cortical connections (11). Hence, it is interesting to note the significant negative correlation between the GI and the duration of illness. Indeed, various studies have implicated thalamo-cortical connections in the pathophysiology of schizophrenia (91-93). Based on the preceding arguments, we suggest that the negative correlation observed in the present study reflects the long-term instability in information processing and the failure of associative mental processes across the years of illness in schizophrenia.

This study is limited by the use of the GI only. Further studies should investigate GI along with cortical thickness in order to have a better estimate of gray matter density. We emphasize that our results are preliminary and that larger studies are necessary to confirm our findings. Notwithstanding these limitations, there are two major differences between the present technique and other contemporary image analysis methods, which add to our confidence in interpreting the data: first, we used a completely automated method to assess GI. An advantage of an automated method is that rater error is not a factor and is corrected for multiple threshold. Second, we first used the MNI_AutoReg, which performs a 9-parameter, linear registration to the registration target model in order to later bring native (original raw) images into MNI-Talairach space. Then during the 16th stage of the Civet pipeline "non-linear surface registration" stages—where the cortical surfaces are produced—they need to be aligned with the surfaces of other brains in the data set so cortical morphology data could be compared across subjects. Following this, Surfreg performs a non-linear registration of the surfaces to a pre-defined template surface. These steps are crucial to resampling in native space, which is essential when working with schizophrenia brains. Note that while the vertices have been aligned, the topological measurements associated with them (e.g., GI) remain unchanged in this process. Finally, as gyrification decreases in both healthy controls and patients, it becomes a much more ambiguous marker as it is difficult to isolate factors of gyrification decline with healthy aging and even more so with disease (confounded by disease progression, different behavioral factors, and substance/medication exposure). For instance, future research capturing cortical folding measures prior to or at the time of disease onset may help clarify what brain effects are due to early development versus secondary effects of disease.

In essence, we reported significant sex differences in GI decreases in schizophrenia, which correlated negatively with age and the duration of illness. Since alterations in cerebral development and connectivity may be observed by GI, we advance that this decrease is in accord with the agreed upon neurodevelopmental hypothesis of disconnectivity (5). In conclusion, we emphasize the importance of sex differences in schizophrenia.

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