Altered surface area covariance in the mentalizing network in schizophrenia: Insight into theory of mind processing

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Abstract

Background: Theory of mind (ToM), the cognitive capacity to attribute mental states to self and others, is robustly affected in schizophrenia. The neural substrates of ToM impairment have been largely studied with functional imaging but little is known about structural abnormalities. We compared structural covariance (between-subjects correlations of brain regional measures) of magnetic resonance imaging (MRI)-based cortical surface area between schizophrenia patients and healthy controls, and between schizophrenia sub-groups based on their ToM ability to examine ToM-specific effects on structural covariance in schizophrenia.

Methods: T1-weighted structural images were acquired on a 3T MRI scanner and ToM assessed with the Hinting Task for 104 schizophrenia patients and 69 healthy controls. The sum of surface area was computed for twelve regions of interest selected and compared between groups to examine structural covariance within the often reported "mentalizing network": rostral and caudal middle frontal gyrus; inferior parietal lobule; precuneus; middle and superior temporal gyrus. High and low ToM groups were defined using a median split on the Hinting Task.

Results: Cortical surface contraction was observed in the schizophrenia group, predominantly in temporo-parietal regions. Schizophrenia patients also exhibited significantly stronger covariance between the right rostral middle frontal gyrus and the right superior temporal gyrus than controls ($r = 4.015$; $p < 0.001$). Direct comparisons between high and low ToM sub-groups revealed stronger contralateral fronto-temporal covariances in the low ToM group.

Conclusions: Our results provide evidence for structural changes underlying ToM impairments in schizophrenia that need to be confirmed to develop new therapeutic perspectives.

Introduction

Social cognition is significantly impaired in schizophrenia, linked to neurocognitive performance, and represents an important determinant of functional outcomes (1-3). Social cognition deficits are robustly detected in early-stage or first-episode (FEP) psychosis and are comparable in magnitude to deficits in multi-episode psychosis (4, 5). Theory of mind (ToM; the cognitive capacity to attribute mental states to self and others) is one of the most consistently affected social cognitive subdomains in schizophrenia (6). In the functional neuroimaging literature, several studies have examined the underlying neural substrates of ToM in the general population and have consistently revealed a "mentalizing network" including posterior temporal sulcus/temporoparietal junction (TPJ), temporal pole and medial prefrontal cortex (mPFC; 7). More recently, a large meta-analysis on 144 datasets observed the mPFC and bilateral TPJ were consistently activated regions across several ToM tasks (8). In schizophrenia, a meta-analysis based on 28 studies revealed decreased activations in the frontal part of the mentalizing network and increased activation of bilateral inferior parietal lobule in patients during inference, suggesting circuit disruptions related to ToM impairment (9).

One of the central tenets of neuroscience is that brain function is reflected in changes in brain structure ; however this structure-function association is not one-to-one (10-12). The complexity of structure-function relationships has been highlighted in recent work on the coupling strength between brain structure and function showed that higher cognitive processes, including social cognition, may have structure-function decoupling, meaning that functional signals are not as dependent as expected on the underlying anatomical structure (13). These complex relationships underscore the need for more brain morphometric imaging studies to evaluate the structural correlates of ToM and see whether structural abnormalities map onto functional networks previously defined in the literature. One specific area of interest would be the investigation of structural abnormalities within the mentalizing network. The few studies that have examined brain morphometry in relation to ToM have focused on voxel-based measures, revealing reduced grey matter density in fronto-temporo-parietal

areas in small schizophrenia patient samples (14-16). Surface-based morphometric measures, such as cortical thickness or surface area, can provide new insights into the neural bases of ToM, as surface-based measurements can more precisely capture cortical morphometry and show distinct developmental trajectories (17). Within the mentalizing network, linear decreases in cortical thickness within mPFC, TPJ, and superior temporal sulcus have been reported from childhood into the early twenties, whereas surface area shows a cubic trajectory in the same regions, peaking in early age and subsequently decreasing into the second decade of life (17). Given the importance of social cognitive development in adolescence, these two cortical measures may reveal differential associations with ToM performance. Surface area may represent a particularly relevant neurodevelopmental marker to better understand ToM impairment in schizophrenia, as it may be less sensitive than cortical thickness to environmental influences such as drug use (18) and illness-related factors (19).

Correlations of these structural measures with ToM performance have been explored in healthy individuals. For example, Rice and Redcay (20) developed a ToM task involving spontaneous descriptions of the beliefs, emotions, and goals of characters during naturalistic videos. Higher scorers on the ToM task had thinner cortex in mPFC, right inferior frontal gyrus, and right TPJ (20). However, the generalizability of this result is unclear, as the two other ToM tasks used in the study were not significantly associated with any structural brain changes. In schizophrenia, global cortical thinning relative to healthy controls has been described, most pronounced in the frontal and temporal lobes (21). Many studies have explored the relationship between brain structure and various cognitive domains, for instance, executive functioning or verbal memory (22), but only three have explored surface-based cortical measures and social cognition in this population (23-25). One explored the association between ToM task performance and indices of grey matter volume and cortical thickness, revealing that ToM behavioral deficits were associated with thinner right anterior temporal lobe in schizophrenia or bipolar participants who experienced psychosis (25). The two other studies used cortical thickness and structural covariance analysis. In Massey *et al.* (24), reduced cortical thickness was observed in regions previously found to contribute to empathy (left inferior frontal gyrus, bilateral

insula, right supplementary motor area, and right temporoparietal junction) but no significant correlation was observed between cortical thickness and cognitive empathy in the schizophrenia group. In Buchy *et al.* (23), decreased facial emotion recognition was associated with increased cortical thickness covariance between the left fusiform area and right superior parietal lobule in early psychosis patients (23). Structural covariance is a statistical framework that interprets interregional correlations in morphology as proxies for structural networks (26, 27). This covariance technique is posited to tap into structural connections between regions, likely due to coordinated development (26). Further, structural covariance may allow us to observe strong relationships with cognitive data (28) and may better capture group differences due to dysconnectivity or compensatory mechanisms in brain networks in schizophrenia (29, 30).

The broad aim of the current study was to better understand whether ToM structural covariance alterations are consistent with functional dysconnectivity in a well-powered schizophrenia sample. We investigated this by defining six regions of the mentalizing network (caudal and rostral middle frontal gyrus, inferior parietal lobule, precuneus, middle temporal gyrus and superior temporal gyrus; 8, 31, 32) and used two main analysis approaches. First, we compared the surface area of each region of interest (ROI) from the mentalizing network between patients and controls. We hypothesized that surface area would be globally smaller in the schizophrenia group when compared to healthy controls, and would show specific reductions in the right caudal and rostral middle frontal and the left middle temporal regions (29, 33). Secondly, we used a covariance analysis of MRI-based cortical surface area measurements to compare structural brain networks between schizophrenia patients and healthy controls. Our study is the first to explore surface area covariance between these ROIs in schizophrenia population compared to controls, so a nondirectional hypothesis was formulated on fronto-temporal and fronto-parietal structural covariance differences between our two groups. Finally, as structural covariance is a between-groups technique, ToM cannot be easily correlated to the networks, so we examined the role of ToM by separating our patient group on their (high versus low)

ToM performance. Compared to the higher ToM group, we expected the lower ToM group to display the structural covariance differences observed in the previous aim, especially with cortical hub regions including the inferior parietal lobule (34, 35).

Methods and Materials

Participants

One hundred and ten patients completed a structural MRI and social cognition task as part of a larger study (36, 37). They were aged between 18 and 50 years and were recruited from inpatient and outpatient units of the Douglas Mental Health University Institute and affiliated community centers. Clinical information on diagnosis, antipsychotic dosage (converted to chlorpromazine equivalents), and duration of illness were collected by medical chart review, or directly confirmed with patients' medical teams. Patients met DSM-IV criteria for schizophrenia or schizoaffective disorder and had an illness duration of at least 3 years. An abbreviated version of the Structured Clinical Interview for DSM-IV Axis I Disorders was administered to all patients to confirm diagnosis. Exclusion criteria included low neuropsychological performance (IQ < 70), lifetime or familial history of neurological conditions, head injury with loss of consciousness, diagnosis of substance dependence in the past three months, and presence of metallic objects in the body.

Seventy-two healthy controls (HC), group-matched for age and sex with no personal or familial history of psychotic illness, were recruited through online advertisements and completed the neuroimaging portion of the study and the social cognition task. The Structured Clinical Interview for DSM-IV-TR Axis 1 Disorders, non-patient version (SCID-NP; 38) was administered to all healthy controls to rule out the presence of any current mental illness.

All participants provided written informed consent and received compensation for their participation. The study procedures were approved by the Douglas Institute Research Ethics Board.

Participants were assessed for socio-demographic data and the Wechsler Abbreviated Scale of Intelligence (WASI-II; 39) was used to quickly and accurately estimate IQ. Handedness was assessed by the Edinburg Handedness Inventory (40). ToM was assessed by an explicit verbal cognitive task, the Hinting task, which examines the ability to infer the true intent of indirect speech (41). Ten short passages presenting an interaction between two characters were read aloud by the experimenter. Each passage ended with one of the characters dropping a hint, and participants explained what the character truly meant (e.g., *Rebecca's birthday is approaching. She says to her Dad, "I love animals, especially dogs." Question: What does Rebecca really mean when she says this?*). If the first response provided was inaccurate, a second hint could be delivered (e.g., *Rebecca goes on to say, "Will the pet shop be open on my birthday, Dad?" Question: What does Rebecca want her Dad to do?*), allowing participants to earn partial credit (1 point out of 2). Total scores range from 0 to 20. In the Social Cognition Psychometric Evaluation project (42), designed to improve the measurement of social cognition in schizophrenia, the Hinting task was recommended for use in clinical trials because of its strong psychometric properties and strong relations with measures of functional outcome, including uniquely accounting for variance in outcomes while controlling for other social cognitive tasks.

MRI acquisition and processing

T1-weighted structural images were acquired on a Siemens 3T Tim trio MRI at the Cerebral Imaging Centre of the Douglas Mental Health University Institute with an MPRAGE sequence (TR=2300ms, TE=2.98ms, FOV 256mm, 1 mm × 1 mm × 1 mm voxels, flip angle=9, scan time~9 min). Quality control was conducted on structural MRI scans checking for motion, abnormal intensity artifacts or incidental findings; through this process, one schizophrenia patients and 3 controls were excluded. Quality-controlled scans were converted from DICOM to MINC format and then submitted to the CIVET processing pipeline to extract surface area (version 2.1.0:

http://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET, Montreal Neurological Institute at McGill University, Montreal, Quebec, Canada; 36, 43, 44).

Processing steps included: 1) registration of T1-weighted images to the ICBM152 nonlinear template and correction for non-uniformity (45, 46); 2) tissue classification (47); 3) extraction of grey and white matter surfaces within 40,962 vertices from each hemisphere (48); and 4) direct computation of the vertex-based areas on the resampled surfaces, measuring local variations of area contraction and expansion relative to the vertex distribution on the surface template. Surface area data were smoothed using a 20-mm kernel (49, 50). A detailed description of the processing steps from our group can be found elsewhere (51). The 6 bilateral ROIs were defined using the Desikan-Killiany-Tourville atlas (DKT; 52): rostral and caudal middle frontal gyrus, inferior parietal lobule, precuneus, middle temporal gyrus and superior temporal gyrus. Delimitations of each ROI are described in Klein and Tourville (52).

All scans processed through CIVET were also visually inspected to ensure the quality of grey/white matter surface extraction, leading to three rejection of patients' scans. MRI scans of 106 patients and 69 controls were retained for subsequent analyses.

Statistical analyses

Descriptive statistics were computed to characterize the groups. Independent samples t-tests were performed to compare sociodemographic data between schizophrenia patients and healthy controls. For each group, we conducted Pearson correlations with the Hinting score and the ROI-based surface area of the 12 selected regions. In the schizophrenia group, we also conducted Pearson correlational analyses between clinical scores (SAPS and SANS global scores, and subscores if the correlation with the global score was significant) and the Hinting task score, as between these clinical scores and the ROI-based surface area. Correlations were conducted with age, sex and IQ as controlling variables and Bonferroni-corrected for multiple comparisons. The total surface area of the brain was added as a covariate when the correlations involved ROI-based surface area. To divide the schizophrenia group

on ToM performance, we used the Hinting task. We obtained the median from our larger database of schizophrenia patients (n=166), which does not rely on the imaging data and allows us to use a larger sample of patients and more accurately separate patients on their Hinting task scores. We then applied this median score to our current smaller sample. The schizophrenia group was separated into 'high scorers' (Hinting score $\geq$ 17; n = 59) and 'low scorers' (Hinting score < 17; n = 45). Analyses of clinical and cognitive variables were conducted using SPSS 23® (SPSS inc., 2009, Chicago, IL, USA), and were two-tailed with a critical *p*-value of 0.05.

Surface area analyses

The 81,924 vertices of the cortical surface were parcellated into ROIs by summing the areas of each vertex falling within a given DKT region matching the desired ROIs (29, 33). The surface area of each ROI was first compared between groups using an ANOVA with a within-subjects factor of hemisphere (left vs right) and a between-subjects factor of group (schizophrenia vs control). The 12 selected ROIs were then used for ROI-to-ROI structural covariance analyses in patients and controls. In a first model, age, sex, and total brain surface area were regressed out of the ROI-based surface area and the residuals were then used to compute pairwise correlations between ROIs for each group separately. A second model was also tested, adding the IQ estimation to the previous covariates (age, sex, total brain surface) in order to examine whether any effects could be explained by a generalized cognitive impairment. For both models, correlation coefficients were compared between groups, using Fisher's *r*-to-*z* transformation. For the patient group, a supplementary covariate was tested in a third analysis to control for medication effects. Chlorpromazine-equivalent antipsychotic dosage was regressed out ROI-based surface area in patients before the between-group comparison was run. The schizophrenia group was then divided into two subgroups based on the Hinting task median score to conduct a structural covariance group comparison between high and low scorers. Similar to the comparison between the schizophrenia group and healthy controls, we used three different models to compare high and low-scorers, using the following sets of covariates: (1) age, sex, and total brain surface area;

(2) age, sex, total brain surface area and IQ; (3) age, sex, total brain surface area, IQ and CPZ-equivalent. The two-step Benjamini, *et al.* (53) FDR procedure was applied to all the covariance analyses to correct for multiple comparisons.

Results

Three outlier patients were excluded due to a score on the Hinting task 3 SD below the mean of the schizophrenia group (<8; 54), indicating a potential failure to understand the task. Sociodemographic and clinical data of the remaining 103 patients and 69 controls are presented in Table 1. The two groups differed on educational level and IQ, with a higher level of education and IQ in the control group than in the schizophrenia group. Scores on the Hinting task were significantly higher in controls than in schizophrenia patients.

The control versus patient group comparison conducted between the surface area of each selected region is presented in Figure 1 and revealed significantly lower surface area in schizophrenia patients compared to controls in the IPL, precuneus, MTG, and STG (Table 2). Total surface area was also globally reduced in schizophrenia patients (214636.38 mm^2 ± 8732.48) when compared to controls (220185.13 mm^2 ± 8411.62; t = -4.152; p <0.001), but no between-region effects remained significant when residuals (covariates: age, sex and total brain surface area) were used for each ROI ($p's$ > 0.120).

Results of the correlational analyses between clinical scores (SAPS and SANS scores) and the Hinting task score, as between these clinical scores and the ROI-based surface area are presented in supplemental material (S1). None of the correlation observed remain significant after Bonferroni correction.

ROI-to-ROI structural covariance

In each group (healthy controls and schizophrenia), FDR-corrected structural covariance between the selected regions is displayed in a supplemental figure (S2). Our analysis exhibited a significantly stronger covariance between the right rostral middle frontal gyrus and the right superior temporal gyrus in the schizophrenia group than in the control group (z = 4.015; p < 0.001; Figure 2, part A and B). The second model adding IQ to the previous covariates revealed similar results (z = 3.975; p < 0.001). Further, chlorpromazine-equivalents were added as a covariate in the schizophrenia group in a second analysis and did not modify the significance of the previously described covariance between patients and controls (z = 4.170; p < 0.001).

Results of the structural covariance analyses comparing the two schizophrenia subgroups based on the Hinting task score (high and low ToM scores) are presented in Figure 3. The first model tested revealed significantly stronger covariance between the right caudal middle frontal gyrus and the left middle temporal gyrus in the low ToM than in the high ToM group (z = -3.916 ; p< 0.001). The second model adding IQ to the previous covariates revealed similar results (z = -4.008; p < 0.001) and an additional stronger covariance between the left caudal middle frontal gyrus and the right superior temporal gyrus in the low ToM score than in the high ToM score group (z = -3.625 ; p = 0.001). The third model adding chlorpromazine-equivalents as a covariate displayed the same differential patterns of structural covariance (z = -4.186 ; p<0.001 and z = -3.504 ; p = 0.002, respectively) and two additional ones: a stronger covariance between the left caudal middle frontal gyrus and the right middle temporal gyrus in the low ToM score than in the high ToM score group (z = -3.366 ; p = 0.003) and a stronger covariance between the left middle temporal gyrus and the left superior temporal gyrus in the high ToM score than in the low ToM score group (z = 3.463 ; p = 0.002).

Discussion

Our objective was to investigate structural network abnormalities within functional mentalizing network in schizophrenia by measuring surface-based structural covariance of previously defined ROIs.

Our approach offers the opportunity to tap into neurodevelopmental processes and potential brain reorganization associated with surface area disruptions across various regions that are strongly associated with social cognition. Our study revealed cortical surface contraction in temporo-parietal regions and stronger covariance between right fronto-temporal areas in a large cohort of schizophrenia patients compared to controls. By dividing our schizophrenia group on the Hinting task score, a consistent stronger covariance between contralateral fronto-temporal areas was driven by patients demonstrating poor ToM performance.

Our results revealed significant surface contraction in schizophrenia patients in temporo-parietal regions belonging to the mentalizing network. Correlations observed between the surface area measures and the clinical symptoms (negative symptoms) were not significant after correction. In a study conducted on 57 schizophrenia patients, a relative areal contraction was observed in the default mode network, which greatly overlaps with regions of the mentalizing network (precuneus, ventromedial prefrontal region, and the angular gyrus of inferior parietal lobe), and multimodal association regions, such as the middle temporal gyrus and the superior temporal sulcus (29). These significant regional area contractions suggest a neurodevelopmental pathological process that would affect cortical expansion, although in our sample, regional group differences did not remain significant after controlling for global surface area. This result is in accordance with the Enhancing Neuro Imaging Genetics Through Meta-Analysis (ENIGMA) Consortium that revealed global cortical surface contraction in a large cohort of schizophrenia patients (n=4474) (21). In this work, surface area was not significantly associated with medication use or symptom severity and its contraction might correspond to a more global and early neurodevelopmental phenomenon than cortical thinning (21).

One of our main result is the stronger covariance observed between right fronto-temporal areas in schizophrenia patients relative to controls. In the general population, these regions are differentially involved in ToM: the prefrontal cortex is involved in ToM processing and handles socially relevant information (55, 56), whereas STG plays a central role in processing social stimuli and contributes to

social knowledge (57, 58). Most brain regions have high covariance with their cross-hemisphere homolog (59), and an inverse relationship exists between the strength of structural covariance and the spatial distance between brain areas (60), meaning that brain area proximity implies higher structural covariance between regions. In our study, a higher covariance was observed between non-homologous regions in schizophrenia patients. The uncovered positive frontoparietal correlation could reflect altered coordination during neurodevelopmental processes shaping both of these regions, such as cell differentiation and proliferation (26). This interpretation is supported by graph theory studies that suggest brain organizational principles are disrupted in schizophrenia (26, 61). Indeed, structural networks of schizophrenia patients have a less optimal topological organization with an altered integration capacity across brain regions (62). And drug therapies do not appear to be responsible for these changes. In the current study indeed, medication did not affect structural covariance. Although antipsychotic treatment has been reported in some studies to be significantly correlated with structural brain changes among schizophrenia patients (63, 64), there were no detectable correlations between chlorpromazine dose equivalents and cortical surface area for any of the regions explored by the ENIGMA consortium (21).

We also sought to understand these results in relation to ToM impairment in schizophrenia by directly comparing structural covariance between high and low ToM score schizophrenia subgroups. Interestingly, our results demonstrated a stronger structural covariance between contralateral fronto-temporal areas in the group that displayed poor ToM performance. These results did not seem to be affected, but instead were made stronger, by the introduction of IQ estimation as a covariate, supporting that our results do not simply reflect a general cognitive impairment found in schizophrenia but might be more specific to sub-domains like theory of mind. Some authors have used data-driven groups to explore the neural bases of cognitive profiles. For example, Kirschner *et al.* (65) found three clinical-anatomical phenotypes, the first one associating cognitive impairments, negative symptoms and tissue volume loss within the default mode network and visual network. With a multimorbid sample of marginalized adults, Gicas *et al.* (66) identified three clusters of patients based on their

cognitive data and structural brain networks. Modularity analysis conducted on a local gyrification index, a measure of cortical folding, revealed four similar modules in each group, including a group characterized by higher right fronto-temporal gyrification compared to other groups. In our work, the covariance between fronto-temporal regions is driven by the patients who had lower ToM performance and thus, stronger impairments in social cognition. As alluded to above and also discussed by Palaniyappan *et al.* (67), a stronger covariance in the patient group could reflect an inefficient reorganization of the brain. In our last model of analysis using chlorpromazine-equivalent as an additional covariate, a stronger left temporal (STG and MTG) covariance was also observed in the schizophrenia subgroup with higher performance on the ToM task. This spatially proximal strengthened covariance may indicate overconnectivity that might reflect a functional adaptation to maintain performance. Indeed, structural reorganization could be advantageous for ToM processing and subsequent functional reorganization, but it could also lead to inefficient recruitment of brain regions unnecessary for the task at hand, and thus prompt inappropriate social information.

Our study has some limitations. Despite a large cohort of patients, we had a slight over-representation of males in both groups. Though this is consistent with the typical increased presentation of males with schizophrenia and our groups were sex-matched, the literature on structural covariance patterns has reported sex differences (59, 68). As such, sex was taken into account in the analyses. Second, despite the significant differences found between high and low scorers once split in half, our sample size can be considered as a limitation and our results should be replicated in another sample to underpin these. Third, we used an ROI-based structural covariance analysis with pre-selected functional ROIs using DKT atlas, which defines quite large brains regions with a risk of missing covariance of more focused ToM-related brain regions. These pre-selected ROIs may also have excluded other structural network abnormalities that might act in parallel. However, we chose a hypothesis-driven approach to reduce the number of multiple comparisons, and increase the statistical power of the tests. Finally, the correlational and indirect nature of the analyses might limit our interpretation of the relationship

between our results and ToM impairments, though our approach is consistent with previous work using the Hinting Task to assess brain measures in schizophrenia (69, 70).

Our findings provide insightful surface-based neuroanatomical results in a large cohort for understanding the neuroanatomical underpinnings of ToM in schizophrenia and offer a starting point for replication studies and future research. For example, multimodal assessment combining structural and functional data would be of interest, as well as longitudinal data in younger patients, to have a more comprehensive view of the neurodevelopmental processes involved in ToM impairment in schizophrenia and confirm our hypotheses. New therapeutic interventions could also be developed, directly using the knowledge on connectivity networks with neuromodulation, or by optimizing social cognitive remediation therapy. Briefly, neuromodulation refers to the changes in activity induced in targeted brain areas via the introduction of either magnetic pulses (e.g. transcranial magnetic stimulation; TMS) or electrical currents (e.g. transcranial direct current stimulation; tDCS). Recent reviews of literature on tDCS (71, 72) reported three studies in schizophrenia population, with 2 of the 3 showing improvements by stimulating the dorsolateral prefrontal cortex (73, 74). Another recent review raises the possibility to combine TMS and a virtual reality intervention to prime brain activity before social cognition intervention in schizophrenia (75). One of the challenges is to determine the appropriate site of stimulation in the schizophrenia population and these interventions would benefit from robust findings on underlying structural and functional mentalizing networks. We could also expect that understanding the pathway of some compensatory mechanisms would help to develop new strategies to regain ToM abilities and improve the social interactions of the population suffering from schizophrenia.

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Disclosures

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Table 1. Socio-demographic and clinical characteristics of the groups.

	SZ (n=103)		HC (n=69)			
	n		n		χ2	p
Sex (female/male)	27/76		21/48		0.366	0.545
Handedness (right/left/ambidextrous)	80/16/7		55/7/7		2.682	0.612
	Mean	SD	Mean	SD	t	p
Age (years)	34.93	8.17	34.19	8.97	0.563	0.574
Education (years)	11.44	2.57	13.48	2.39	-5.249	*<0.001*
IQ score	95.38	14.87	108.84	13.59	-5.999	*<0.001*
Hinting score	16.37	2.75	18.28	1.76	-5.550	*<0.001*
SAPS	6.53	4.38	-	-		
SANS	8.72	3.10	-	-		
Illness duration (years)	12.70	7.70	-	-		
CPZ-equivalent (mg)	761.95	790.57	-	-		

CPZ: Chlorpromazine; HC: healthy controls; SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms; SD: standard deviation; SZ: schizophrenia.

Table 2. Surface area of the six selected ToM regions in schizophrenia patients and controls.

Regions	Controls Area in mm2	SE	Patients Area in mm2	SE	F	p value
rosMFG	5183.033	71.331	5052.253	58.102	2.021	.157
caudMFG	3122.721	56.887	3041.715	46.336	1.219	.271
IPL	6324.452	72.640	6107.884	59.168	5.343	*.022*
Precuneus	4798.991	49.396	4580.104	40.234	11.805	*.001*
STG	6115.019	53.358	5907.681	43.462	9.077	*.003*
MTG	5734.418	58.176	5549.092	47.386	6.101	*.014*

rosMFG: rostral part of the middle frontal gyrus; caudMFG: caudal part of the middle frontal gyrus; IPL: inferior parietal lobule; STG: superior temporal gyrus; MTG: middle temporal gyrus.

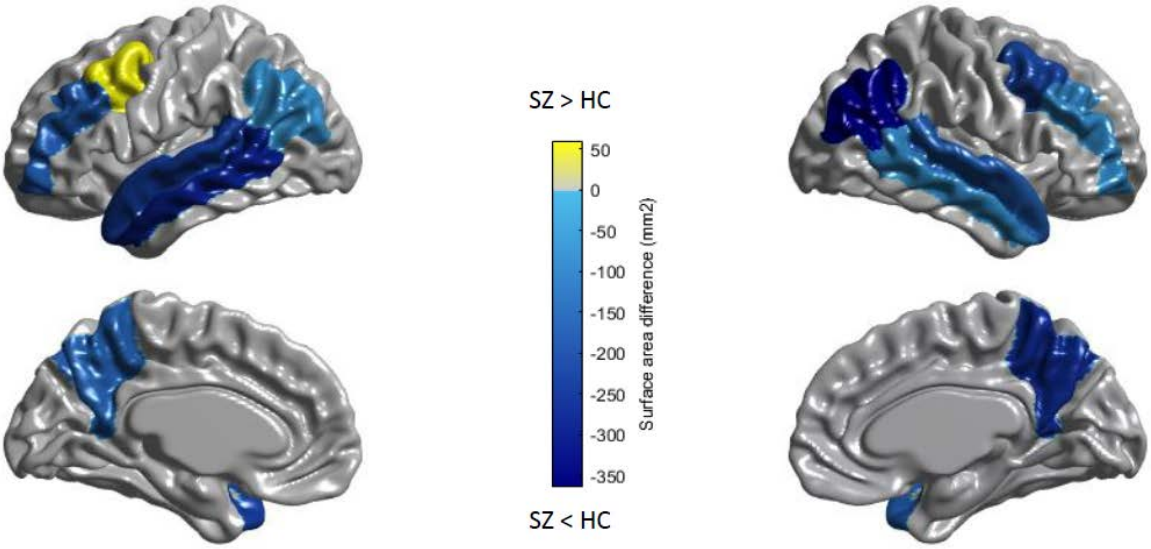

Figure 1. Group differences between the schizophrenia patients (SZ) and the healthy controls (HC) in the surface area (in mm^2) of each of the 12 selected ToM regions.

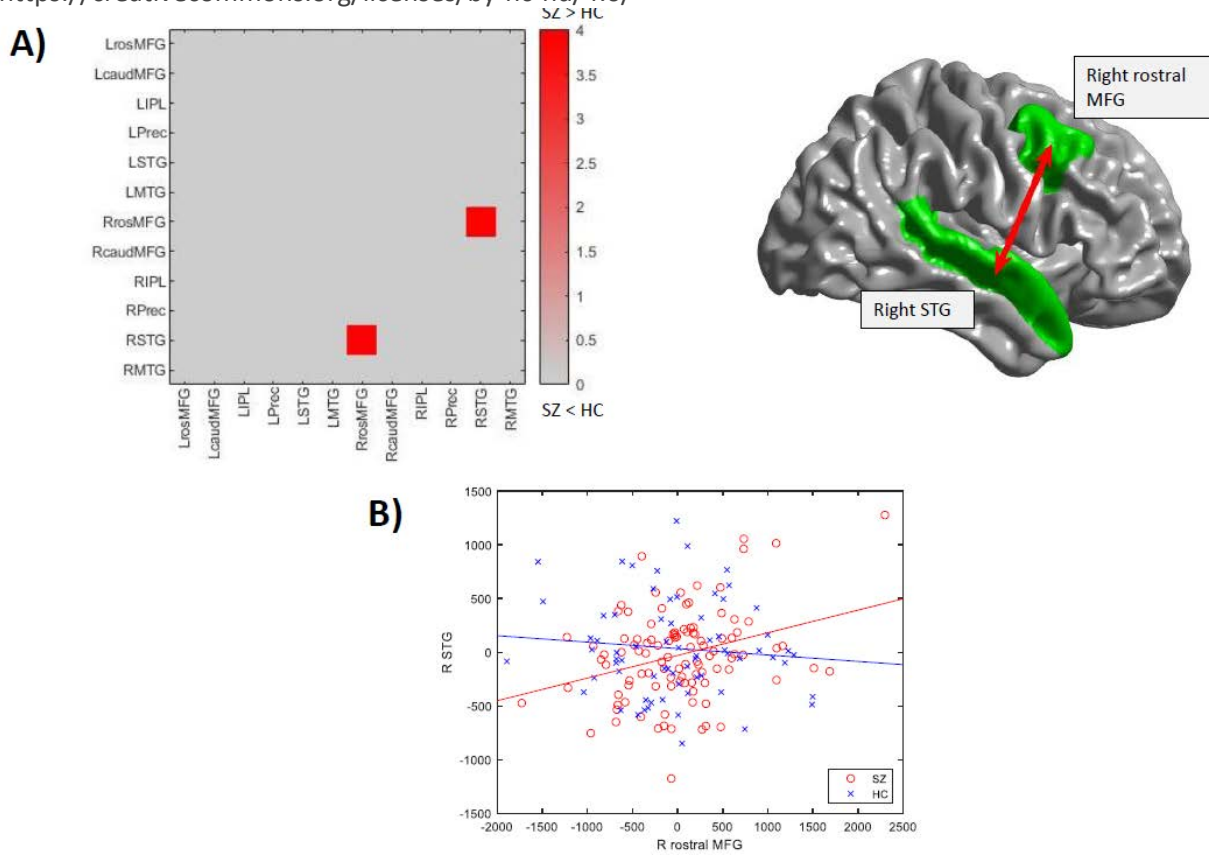

Figure 2. Part A) shows group differences between the schizophrenia patients (SZ) and the healthy controls (HC) in the surface area structural covariance networks across the 12 selected ToM regions. The matrix on the left-hand side displays the z-score differences in pairwise correlation coefficients between groups that survived FDR correction. The brain schematic on the right side represents the significant pairwise regional difference, as depicted in the matrix (MFG: middle frontal gyrus; STG: superior temporal gyrus). Part B) shows the group differences in the right rostral MFG and right STG covariance between SZ and HC.

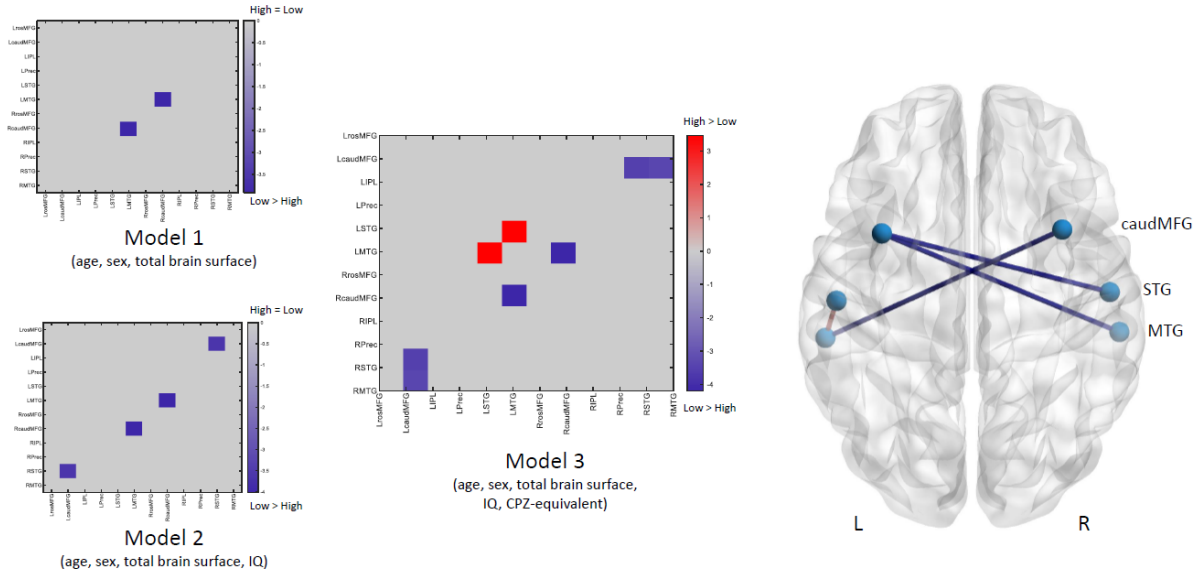

Figure 3. Group differences between the high ToM score (High) and the low ToM score (Low) schizophrenia subgroups in the surface area structural covariance networks across the 12 selected ToM regions.

Matrices on the left-hand side display the z-score differences in pairwise correlation coefficients between groups that survived FDR correction for each model of analysis (covariates are indicated for each model). The “glass brain” schematic was generated with Brain Net Viewer and shows the nodes representing each ROI involved in the significant pairwise regional differences of the third model; the lines connecting the nodes represent the significant pairwise regional differences. Abbreviations: L: left; R: right; caudMFG: caudal part of the middle frontal gyrus; STG: superior temporal gyrus; MTG: middle temporal gyrus.

Altered surface area covariance in the mentalizing network in schizophrenia: Insight into theory of mind processing

Delphine Raucher-Chéné, Katie M. Lavigne, Carolina Makowski, Martin Lepage

Supplemental material S1. Results of the correlational analyses between clinical scores (SAPS and SANS scores) and the Hinting task score and between these clinical scores and the ROI-based surface area.

In the control group, the Hinting score was negatively correlated to the surface area of the left rostral middle frontal gyrus (r = -0.255, p = 0.038) and positively correlated with the surface area of the right middle temporal gyrus (r = 0.255, p = 0.038). In the schizophrenia group, no significant correlation was found between the Hinting score and the ROI-based surface area of the selected regions.

In the schizophrenia group, the Hinting score was negatively correlated to the SANS affect subscore (r = -0.217, p = 0.030) and a tendency was observed with the alogia subscore (r = -0.189, p = 0.060). No correlation was found with the SAPS (*ps* > 0.265). The global SANS score correlated negatively with the surface area of the right STG (r = -0.245, p = 0.012). The alogia subscore correlated positively with right precuneus (r = 0.265, p = 0.007) and the avolition subscore correlated negatively with the right rostral MFG (r = -0.244, p = 0.013) and the right STG (r = -0.254, p = 0.010). None of the correlations survived to Bonferroni correction.

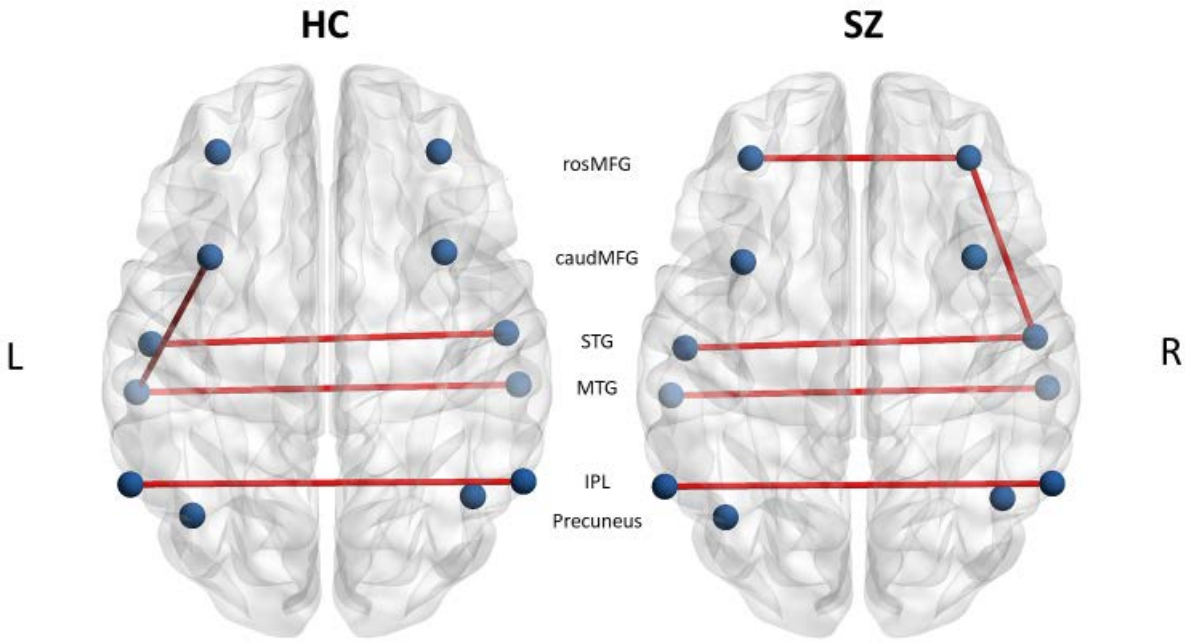

Figure S2. Surface area structural covariance networks across the 12 selected ToM regions in the healthy control (HC) and schizophrenia (SZ) groups.

The "glass brain" schematics were generated with Brain Net Viewer and show the 12 nodes representing each selected ROI; the lines connecting the nodes represent significant pairwise regional differences. Abbreviations: L: left; R: right; rosMFG: rostral part of the middle frontal gyrus; caudMFG: caudal part of the middle frontal gyrus; STG: superior temporal gyrus; MTG: middle temporal gyrus; IPL: inferior parietal lobule.