Cortica

www.revuecortica.net | ISSN : 28131940

Cortica Article
Cortica 2022. *1*(2), 493-530
https://doi.org/10.26034/cortica.2022.3137

Sex differences and symptom based gray and white matter densities in schizophrenia

Adham Mancini-Marïe M.D., M.Sc., Ph.D[a,b,c], Cherine Fahim M.Sc., Ph.D. [b,d,e], Stéphane Potvin M.A., Ph.D.[a,b], Jose Jiminez M.D., M.Sc. [a,b], Nadia Lakis M.Sc.[a,b], Emmanuel Stip M.D., M.Sc., CSPQ, FRCPC [a,b], *Adrianna Mendrek Ph.D.[a,f]

a- Department of Psychiatry, Montreal University Institute for Mental Health (IUSMM), Louis-H Lafontaine Hospital, University of Montreal, Montreal, Quebec, Canada.

b- Department of Psychiatry, Faculty of Medicine, University of Montreal, Montreal, Quebec, Canada.

c- Centre Neuchâtelois de Psychiatrie, Neuchâtel, Switzerland

d- Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada

e- CHU Sainte-Justine, Axe Maladies du cerveau, Université de Montréal.

f- Bishop's University, Sherbrook, Quebec, Canada.

***Auteur correspondant** : Prof, Dr Adrianna Mendrek, Department of Psychology, Bishop's University
Email: amendrek@ubishops.ca

Citation : Mancini-Marie, A., Fahim, C., Potvin, S., Jiminez, J., Lakis, N., Stip, E., Mendrek, A. Sex differences and symptom based gray and white matter densities in schizophrenia. Cortica 2022.*1*(2), 493-530 https://doi.org/10.26034/cortica.2022.3137

Résumé

Nous avons étudié l'association entre les phénotypes des densités dans matière grise (GMD) et de la substance blanche (WMD) et les symptômes positifs (PS) et négatifs (NS) chez 40 patients schizophrènes (SZ). Les densités cérébrales ont été comparées à 41 témoins normaux (NC) appariés pour l'âge et le sexe en utilisant la morphométrie à base de voxel sur d'images IRM T1-3T. Nous avons constaté une diminution de la GMD dans le gyri cingulaire-temporal antérieur et une augmentation de la GMD dans le gyrus cingulaire postérieur en SZ par rapport à NC. Une réduction des WMD a été observée dans les régions frontal inferieur et pariétales postérieures chez le SZ par rapport à la NC. La GMD dans l'insula/caudate était corrélée avec les scores PS, tandis que la GMD dans le gyrus frontal moyen et le cervelet étaient en corrélation avec les scores. Le WMD dans les régions frontales moyennes et frontales supérieures étaient corrélées avec les scores de PS et le NS respectivement. Des corrélations inverses ont été trouvées entre la GMD dans le lobe pariétal et la vermis avec

Cortica
www.revue-cortica.net | ISSN : 2813-1940
Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

les scores PS. Une corrélation inverse a été trouvée entre la GMD dans le cervelet et les scores NS. Une corrélation inverse a également été trouvée dans les WMD de la région occipitale et des régions frontales supérieures avec les scores de PS et NS respectivement. La comparaison entre les groupes hommes a révélé une diminution du GMD total chez les patients hommes, tandis qu'aucune différence n'a été observée entre les groupes femmes. Ces résultats corrélationnels suggèrent que les profils de symptômes dans la schizophrénie montrent des phénotypes GM / WM uniques

Mots clés : schizophrénie, symptômes positifs et négatifs, densité de matière grise et blanche, morphométrie à base de voxel.

Abstract

We investigated the association between phenotypes of gray matter density (GMD) and white matter (WMD) phenotypes and positive (PS) and negative (NS) symptoms in 40 schizophrenia patients (SZ). Cerebral densities were compared with 41 normal controls (NC) matched for age and sex using voxel-based morphometry on T1-3T-MRI. We found decreased GMD in the anterior cingulate-temporal gyri and increased GMD in the posterior cingulate gyrus in SZ relative to NC. We found WMD reduction in the inferior frontal and posterior parietal regions in SZ relative to NC. GMD in the insula/caudate correlated with PS scores, while GMD in the middle frontal gyrus and cerebellum correlated with NS scores. WMD in the middle frontal and superior frontal regions correlated with PS scores and NS scores respectively. We found invers correlations between GMD in the parietal lobe and the uvula with PS scores. We found an inverse correlation between GMD in the cerebellum and NS scores. We also found an inverse correlation in the WMD of the occipital region and superior frontal regions with PS and NS scores respectively. Comparison between male groups revealed decreased total GMD in male patients, while we observed no differences between female groups. These correlational findings suggest that symptom profiles in schizophrenia show unique GM/WM phenotypes.

Keywords: schizophrenia, positive and negative symptoms, gray and white matter density, voxel based morphometry.

1. Introduction

Schizophrenia is thought to be underpinned by neurodevelopmental abnormalities of brain gray matter and white matter function, structure and connectivity (Jablensky, 2010). To date, schizophrenia patients are mainly diagnosed using subjective criteria of psychiatric diagnostic manuals (DSM and ICD). These definitions emphasize the co-occurrence of positive symptoms (PS) (i.e., hallucinations, delusions, and paranoid ideation), and negative symptoms (NS) (i.e., poverty of thought and loss of motivation) (Kay

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

et al., 1987). These definitions are markedly heterogeneous and patients diagnosed with schizophrenia do not necessarily share common symptoms. There is increasing clinical evidence that schizophrenia is a disorder of integration of information between specialized brain regions.

There are well established findings of anatomical differences in GM and WM in patients with schizophrenia. Notable findings are reported for the prefrontal cortex (including the anterior cingulate), the superior temporal gyrus, the limbic system (medial temporal lobe, hippocampus, entorhinal cortex, and amygdala) as well as in the basal ganglia, insula, the thalamus, and the cerebellum (Alemán-Gómez et al. 2020, Sepede et al., 2014). The heterogeneity of the findings do not easily allow for a parsimonious or singular anatomic substrate for schizophrenia phenotypes.

To date, among the most robust biological markers of pathology in schizophrenia are the alterations in brain structure correlated with symptoms detected using magnetic resonance imaging (MRI). An attempt to correlate each of these brain regions to specific symptoms might help advance our way to discovering true endophenotypes. Additionally, the identification of GM and WM structural correlates with symptomatology comparing between/within schizophrenia and other brain disorders might unveil the underlying genetic and pathophysiological bases and pinpoint better-tailored therapeutic targets. For example, the analysis of the National Institute of Mental Health, Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial, stated that NS have greater impact on functioning than PS because of their undetermined etiology and resistance to treatment (Kring et al., 2013). Grouping patients by specific genetic, neuroanatomical and symptoms endophenotypes (Jablensky, 2006) may yield more specific findings.

Sex differences have an important impact on symptoms in schizophrenia. Ochoa et al, (2012) report higher incidence of schizophrenia in men, as well as phenomenological differences by gender. The presence of negative symptoms in males with schizophrenia compared to females is a consistent finding in the literature, and is typically twice as severe in males than in females (Zhao et al., 2022; Andreasen et al., 1990; Chang et al., 2011; Ring et al., 1991). The stability of positive and negative symptoms has been also shown to be affected by the sex of patients. Mancevski and colleagues (2007) reported significant decreases in positive symptoms and increases in negative symptoms over the course of the illness, which were particularly pronounced in males. Neurostructural differences in males and females with schizophrenia have also been reported. Imaging studies on sex–dependent brain

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

abnormalities have consistently reported more severe disturbance in males than in females with schizophrenia: these include reduced prefrontal volumes, reduced anterior temporal horn and medial temporal lobe volumes, more specifically amygdala, hippocampus, superior temporal and larger ventricular-brain ratios (VBR) (Andreasen et al., 1990; Gur et al., 2000). Few studies address the relation between differences in brain structure and symptoms in males and females.

Our group has studied the relation between cortical gyrification and symptoms in males and females with schizophrenia (Mancini-Marie et al., 2018). Our results showed that male schizophrenia patients had inverse correlations between the cortical gyrification index (GI) in the left occipital cortex and negative symptoms, while female patients had positive correlations between GI in the right occipital cortex and negative symptoms. In addition, we observed more severe cortical abnormalities in male patients. We found an important and unanticipated result, the fact that symptoms correlated only with the cortical gyrification of the occipital lobe, while abnormalities in cortical gyrification in our group of schizophrenia patients in comparison to normal controls were observed in several other cerebral regions.

The main purpose of the present study was to investigate the relation between schizophrenia symptoms and gray and white matter densities and the effect of sex on this relation using DARTEL- voxel-based morphometry. In this paper, the term "density" refers to the concentration of GM within a region. We use "voxels" to express concertation/density values. Voxels based Morphometry uses probabilistic segmentation established from histological and partial volume effects that indirectly reflects both neuronal density and myelination (Eickhoff et al. 2005) We hypothesized that grey and white matter structures would be associated with symptoms of schizophrenia and that this relation would show sex differences. We expected changes in fronto-limbic structures to be differentially associated with PANSS scores. Particularly, we hypothesized that (1) gray and white matter densities in fronto-limbic region would differ between schizophrenia patients and normal controls, (2) these regions would differ in relation to the PANSS positive versus negative symptoms and that (3) males with schizophrenia would show more sever grey and white matter abnormalities than females with schizophrenia.

2- Methods

2.1 Participants

Eighty-one subjects were included in this study: 41 normal controls (NC) (22 males [NC-M] and 19 females [NC-F]) and 40 individuals SZ diagnosed with schizophrenia (SZ) (20 males [SZ-M] and 20 females [SZ-F]) according to DSM-IV criteria (American

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

Psychiatric Association, 2000). All patients were in a stable phase of their illness (defined as no relapse within the last two months and no change in their antipsychotic treatment within the last month). The groups were matched for age, sex, handedness (Edinburgh Inventory) (Oldfield, 1971) and parental socioeconomic status (National Occupational Classification (NOC).

There was no significant difference in age between NC (mean age=31.51, SD=7.88) and SZ (mean age=32.08, SD=6.96), p=0.735. In addition, we found no significant differences between male groups or female groups. NC-M had a mean age of 30.50, SD=7.85 (p=0.677), NC-F aged 32.68 SD=7.96 (p=0.988).

Experienced psychiatrists reevaluated all patients before being assigned to the research group according to DSM-IV criteria. We excluded affective, schizoaffective, and schizophreniform psychoses. Control participants were screened with the non-patients edition of the Clinical Interview for DSM-III (SCID) (Spitzer et al., 1992). The positive and negative syndrome scale (PANSS) was used to rate symptom severity (Kay et al., 1987; Kay et al., 1988). The date of illness onset was defined as the date of 1st psychiatric consultation, for lack of reliable information from family members and patients. Schizophrenia has common symptoms with other psychiatric disorders, such as bipolar disorder, personality disorders, etc., therefore a psychiatric consultation favors a better diagnosis. All the patients received at least one atypical antipsychotic (chlorpromazine equivalence was calculated) (Woods, 2003).

General exclusion criteria included: age below 18 or above 45 years, past or present neurological or Axis-I psychiatric disorder, alcoholism or drug abuse, noncompliance with testing procedures, abnormal uncorrected vision, or any contra-indication for MRI such as a cardiac pacemaker, an aneurysm clip, a metal prostheses or cardiac valve replacement, the presence of metal in an eye or any part of the body, certain dental work, or claustrophobia.

In agreement with the Declaration of Helsinki, written informed consent was obtained prior to participation in the experiment. The ability of schizophrenia patients to give informed consent was established using the guidelines of the Canadian Psychiatric Association. The ethics committees of the Fernand-Seguin Research Center of the Louis-H Lafontaine Hospital and the Regroupement Neuroimagerie Québec approved the study. Full details of subject characteristics are given in Table 1.

All normal control participants were medication naïve, with no history of neurological or psychiatric disease. No abnormalities were observed on their brain structural MRIs.

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

Table 1. Demographics of schizophrenia patients

	Males Mean (SD)	Females Mean (SD)	P value df=38
Age	31.50 (7.55)	32.65 (6.46)	0.608
Years of education	11.20 (2.06)	12.25 (3.47)	0.253
Age of onset	19.89 (2.97)	24.40 (7.75)	0.007
Duration of illness (years)	11.57 (7.74)	8.25 (5.70)	0.136
Parental socio-educational status	2.82 (.612)	2.62 (1.06)	0.470
Chlorpromazine equivalence	722.50 (383.74)	443.33 (280.94)	0.012

For high definition images please see annex

2.2 Image acquisition

Eighty-one individual high-resolution co-planar anatomical images were acquired using an 12-channel headcoil (three-dimensional, spoiled gradient echo sequence; sagittal orientation, slices=176, scan time 9:38 min, slice thickness=0.98 mm, TR=19 ms, TE=4.92ms, flip angle=25°; matrix 256x256 voxels, FOV: 256x256 mm, isotropic voxels 1.0 x 1.0 x 1.0mm) on a MRI Siemens TRIO-TIM system (Total Imaging Matrix) at 3.0 Tesla operating at the University of Montreal Geriatric Institute.

2.3 Image and statistical analyses

Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology) implemented in MATLAB R2010a (Mathworks, Sherborn, MA) was used for image analyses. Images were converted to NIFTI format and processed using SPM8.

All 81 subjects passed the SPM8 data quality control. Images were analyzed using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) toolbox in SPM8 used for voxel-based morphometry (VBM). We used VBM to assess the voxel-wise comparison of the local concentration/volume of GM and WM between groups (NC and SZ), then within the SZ (multiple-regression with the PANSS).

DARTEL toolbox uses a high dimensional warping process that increases the registration between individuals, which results in improved localization and increased sensitivity in analyses (Ashburner, 2007). Processing begins with the “import” step. This involves taking the parameter files produced by the segmentation, and writing out rigidly transformed versions of the tissue class images, such that they are in as close alignment as possible with the tissue probability maps. The second step is the registration itself. It involves the simultaneous registration of GM with GM and WM with WM. This procedure begins by creating a mean of all the images, which is used as an initial template. Deformations from this template to each of the individual images are computed, and the template is then re-generated by applying the inverses of the deformations to the images and taking their average. Following this, warped versions of the images can be generated. These steps improve computational anatomy providing more easily interpreted voxel-based morphometry (VBM), and better parameterization of brain shapes. The normalized gray matter GM and WM maps were then modulated with the resulting

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

Jacobian determinant maps and smoothed with an 8-mm FWHM Gaussian kernel.

Total GMD, WMD and total brain volume were obtained from calculated raw volumes in the VBM8 toolbox. The segmented images were visually inspected, then imported to DARTEL for warping procedure, and finally iteratively aligned to the average template. During DARTEL warping, the segmented images were modulated with Jacobian determinates to preserve volume changes. Expert users carefully evaluated each step to check for normalization or segmentation errors. For more details please refer to Ashburner et al., (2007, 2009) and http://www.fil.ion.ucl.ac.uk/spm/software/spm8/SPM8_Release_Notes.pdf

In SPM8 VBM, all statistical analyses used the general linear model (GLM), which is used to identify regions of GM and WM concentration/volume that are significantly related to a specific variable (Ashburner et al., 2001). We conducted an exploratory whole-brain analysis. VBM is not biased to one particular structure, which permits an even-handed and comprehensive assessment of anatomical differences throughout the brain (Ashburner et al., 2001). All reported brain regions were examined at a threshold corrected for multiple comparisons (FWE-corrected at cluster-level, $p<0.05$). All coordinates are reported in Montreal Neurological Institute (MNI) format. Using the tool Talairach Applet (http://www.talairach.org/applet.html) the anatomic location of significant clusters was detected. We used SPM to perform group structural differences and to perform exploratory whole brain correlation analyses with PANSS positive and negative symptoms.

2.4 Automatic Linear Modeling (ALM)

We further conducted a prediction model using the Automatic Linear Modeling (ALM) in SPSS21.

We fitted an ALM for GMD and WMD separately with covariates as age, sex, duration of illness, age of onset, medications,

cognitive scale measures (Raven percentile, Wechsler Adult Intelligence Scale (WAIS), all positive PANSS symptoms and all negative PANSS symptoms. We performed separate regression analyses of total GMD and WMD on the best linear unbiased predictors. To that end, we used the forward stepwise approach combined with the Akaike's Information Criterion Corrected (AICC) (Hurvich et al., 1995). We applied the best subset that checks "all possible" models, or at least a larger subset of the possible models than forward stepwise, to choose the best according to the best subsets criterion. The model with the greatest value of the criterion is chosen as the best model. Then, we applied the adjusted R-squared so that any effects in the model that correspond to a decrease in the prediction model are removed (i.e., $p<0.05$).

Cortica
www.revue-cortica.net | ISSN : 2813-1940

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

3. Results

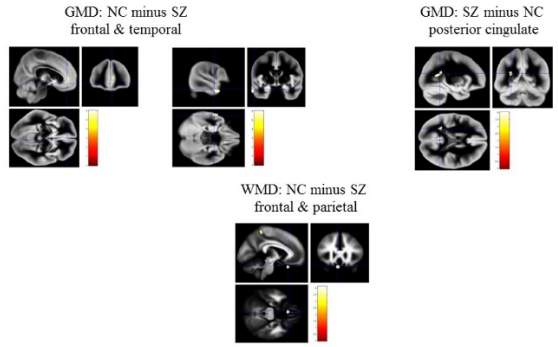
3.1 Imaging results

SZ showed lower gray matter densities in the anterior cingulate cortex and left middle temporal region, and higher GMD in the left posterior cingulate, relative to NC. Moreover, SZ had significantly lower WMD in the left inferior frontal and the left posterior parietal regions in comparison to NC (Table 2; Figure 1).

Table 2. Regions of gray and white density differences between the schizophrenia group and normal controls based on voxel-based morphometry analyses

	Brain region	K (voxels)	t ($p<0.05$ $P_{FDR-\ corr}$) MNI coordinates
GMD NC > SZ	Anterior cingulate cortex (BA32)	336	6.02 (0, 44, 10)
	Middle temporal cortex (BA21)	373	5.97 (-59, -1, -21)
GMD SZ > NC	Posterior cingulate	230	4.02 (-30, -63, 16)
WMD NC > SZ	Inferior frontal lobe	130	4.12 (-6, 21, -23)
	Posterior parietal lobe	138	3.72 (-9, -48, 66)

Figure 1. T-Statistic maps of the group effects between schizophrenia patients and normal controls
Hot and yellowish colors indicate density increases and decreased in each group.



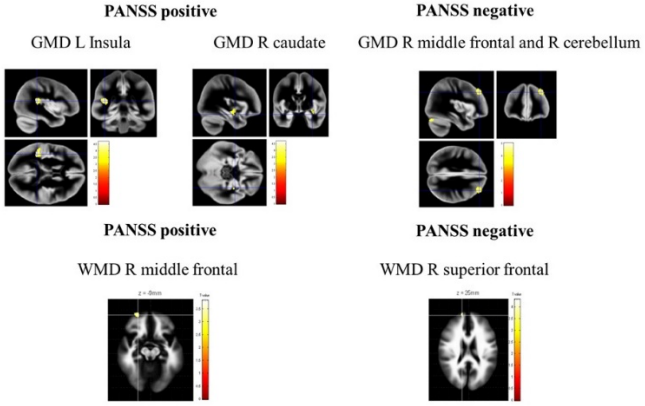
For high definition images please see annex

We observed significant positive correlations ($p<0.05$) between PS scores and GMD in the left insula and right caudate; and between NS scores, the right middle frontal, and the posterior lobe of right cerebellum (uvula) (Table 3, Figure 2).

Table 3. Positive correlations between GMD and WMD regression analysis based on symptoms scores (all results are $p<0.05$, $P_{FWE-\ corr}$).

GMD	Region	K	T	MNI
PANSS positive scores	L Insula	523	4.68	-42, -42, 18
	R Caudate	195	4.21	35, -16, -9
PANSS negative scores	R Middle Frontal	467	5.03	38, 36, 42
	R Cerebellum posterior lobe Uvula	206	4.57	39, -84, -21
WMD	**Region**	**K**	**T**	**MNI**
PANSS positive scores	R Middle frontal	240	3.82	27, 57, -8
PANSS negative scores	R superior frontal	72	4.32	14, 56, 24

Figure 2. Positive correlations between GMD and WMD regression analysis based on symptoms



For high definition images please see annex

We found inversed significant correlations between PS scores and GMD both the right parietal (precuneus), and the posterior lobe of left cerebellum (uvula).

Additionally, we found inversed correlations between NS scores and the anterior lobe of the left cerebellum. Concerning WMD, we found positive correlations with PS scores in the right middle frontal region, while NS scores were positively correlated with WMD in the right superior frontal region. PS scores

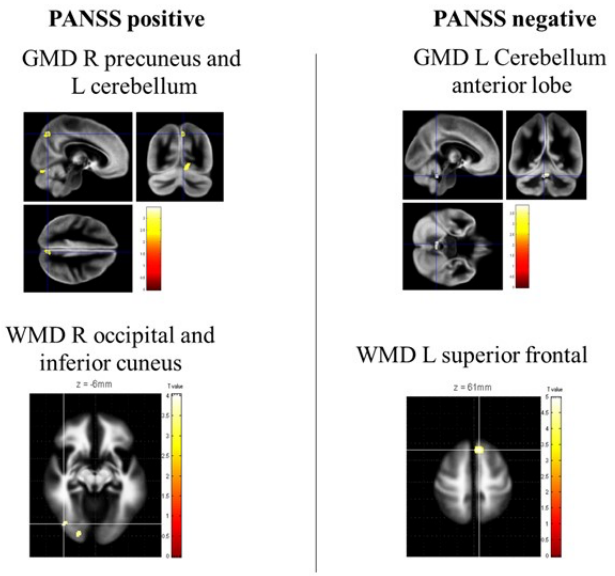
Cortica
www.revue-cortica.net | ISSN : 2813-1940
Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

correlated negatively with the right inferior occipital, and the right occipital cuneus. NS scores correlated negatively with the left superior frontal (Table 4, Figure 3).

Table 4. Negative correlations between GMD and WMD regression analysis based on symptoms scores (all results are p<0.05, $P_{FWE-corr}$).

GMD	Region	K	T	MNI
PANSS positive scores	R Parietal lobe precuneus	125	-3.04	6, -72, 52
	L Cerebellum posterior lobe Uvula	219	-3.45	-9, -88, -21
PANSS negative scores	L Cerebellum anterior lobe	106	-3.87	-5, -52, -23
WMD	**Region**	**K**	**T**	**MNI**
PANSS positive scores	R Inferior occipital	124	-4.03	44, -82, -8
	R Cuneus occipital	145	-3.88	21, -94, -2
PANSS negative scores	L superior frontal	311	-4.97	-8, 18, 60

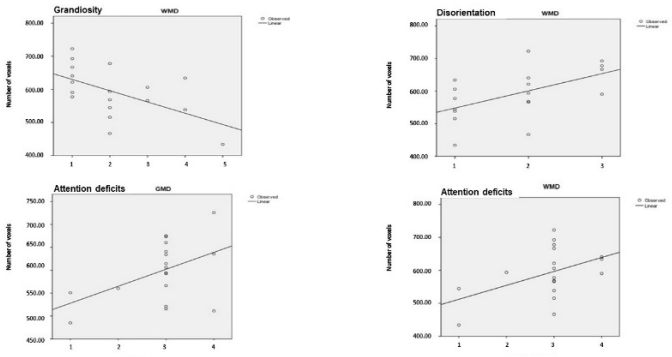
Figure 3. Negative correlations between GMD and WMD regression analysis based on symptoms



For high definition images please see annex

Comparison between male groups revealed decreased total GMD (F=.126 t=2.217 df =40 p=.32) while no such differences were observed in the corresponding contrast for females. SZ-F showed no correlation between total GMD, WMD, CSF, or total brain volume and schizophrenia symptoms. SZ-M showed inverse correlations between ideas of grandiosity and WMD (r=-.551, r2=.303, t=-2.639, p=.018, df=38). Additionally, SZ-M showed positive correlation between disorientation and WMD (r=.545, r2=.297, t=2.598, p=.019, df=38), attention deficits and GMD (r=.466, r2=.217, t=2.108, p=.05) and attention deficits and WMD (r=.463, r2=.214, t=2.089, p=.05, df=38) (Figure 4).

Figure 4. Regression analyses in males with schizophrenia and symptoms



For high definition images please see annex

Legend Figure 4. Regression analyses in males with schizophrenia and symptoms

We found negative correlation between ideas of grandiosity and WMD (r=.551, r2=.303, t=-2.639, p=.018) in male patients. We also found positive correlations between disorientation and WMD (r=.545, r2=.297, t=2.598, p=.019), and attention deficits and GMD (r=.466, r2=.217, t=2.108, p=.05) and WMD (r=.463, r2=.214, t=2.089, p=.05).

We further conducted an exploratory prediction model of the linear regression relationship between GMD and WMD with the PANSS symptoms scores respectively in all patients. We note that they share the conceptual disorganization symptom, which is positively correlated with both structures

Cortica
www.revue-cortica.net | ISSN : 2813-1940
Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

(GMD: coefficient=38.99; F=5.43; p<0.026 and WMD: coefficient=41.69; F=7.53; p<0.010). Conversely, we note that GMD was negatively correlated with lack of spontaneity (F=6.10; t=-2.50; p<0.020) and hallucinations (F=5.89; t=-2.43; p<0.021). WMD was negatively correlated with hostility (F=5.80; t=-3.12; p<0.01) and grandiosity (F=7.82; t=-2.80; p<0.01) (Figure 5 and 7).

The intensity of lack of spontaneity (p=0.019) and hallucination (p=0.021) symptoms predicted the degree of GMD loss, while increased hostility (p=0.007) and grandiosity (p=0.008) symptoms predicted decreased WMD. Interestingly, the intensity of conceptual disorganization was a predictor factor of increased GMD (p=0.026) and WMD (p=0.10) in SZ (Figure 6 and 8).

Figure 5. Model prediction by importance: ALM results
Coefficients
Target: Grey Matter Densities

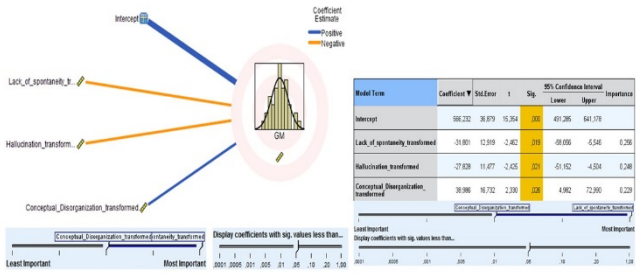


Figure 6. Model prediction by importance: ALM grey matter results

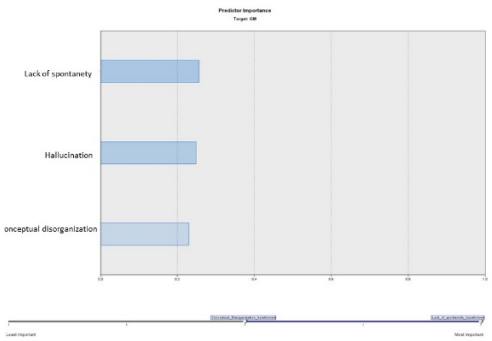


Figure 7. Model prediction by importance: ALM results
Coefficients
Target: White Matter Densities

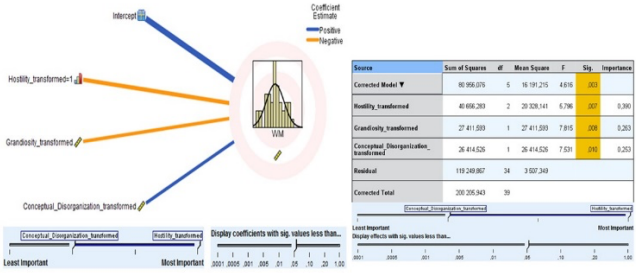
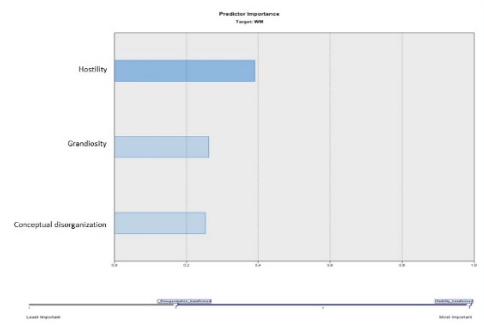


Figure 8. Model prediction by importance: ALM white matter results



For high definition images please see annex

Legend Figure 5 and 7. Model prediction by importance: ALM results

The ALM predicted the continuous target (GM) based on linear relationships between the target and all included predictors by importance. The results reveal three important predictors of gray matter densities: lack of spontaneity and hallucination, and conceptual disorganization. Lack of spontaneity and hallucination predicted lower gray matter densities. Conceptual disorganization predicted increased gray matter densities.

For high definition images please see annex

Legend Figure 6 and 8. Model prediction by importance: ALM results

The ALM predicted the continuous target (WM) based on linear relationships between the target and all included predictors by importance. The results reveal three predictors by level of important of white matter densities: hostility, grandiosity, and conceptual disorganization. Increased hostility and grandiosity scores predicted lower white matter densities. Increased conceptual disorganization scores predicted increased in white matter densities.

Cortica
www.revue-cortica.net | ISSN : 2813-1940

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

3.2 Results of clinical assessments:

We found no differences between SZ-M and SZ-F when using the total PANSS scores of: NS, PS, or general items. When analyses were performed by individual item, we found no differences between SZ-M and SZ-F except on item “Guilt feeling” of the PANSS general, where SZ-F had higher scores (SZ-M: mean=1.67, SD=0.69, SZ-F: mean=2.38, SD=0.96, p=0.018, df=38). We found a trend in the Suspiciousness /persecution item where females had higher symptom score (SZ-M: mean=2.28, SD=1.23, SZ-F: mean=3.25, SD=1.73, p=0.066, df=38)(Table 5).

Table 5. Clinical assessments in schizophrenia patients

	SZ-M Mean (SD)	SZ-F Mean (SD)	P value df=38
PANSS positive	17.95 (5.33)	19.65 (8.03)	0.435
Delusions	3.39 (1.09)	3.31 (1.35)	0.857
Conceptual disorganization	3.06 (0.87)	3.31 (1.30)	0.500
Hallucinations	2.06 (1.23)	3.31 (1.49)	0.941
Excitation/Hyperactivity	2.06 (0.87)	2.25 (1.13)	0.575
Grandiosity	2.11 (1.23)	2.50 (1.59)	0.429
Suspiciousness/persecution	2.28 (1.23)	3.25 (1.73)	0.066
Hostility	1.56 (0.86)	2.21 (1.15)	0.108
PANSS negative	19.50 (5.36)	21.25 (8.30)	0.434
Blunted affect	3.11 (1.02)	3.29 (1.26)	0.868
Emotional withdrawal	3.00 (1.28)	3.38 (0.31)	0.397
Poor rapport	2.72 (1.02)	3.19 (1.52)	0.296
Passive/apathetic	2.61 (1.09)	2.88 (1.15)	0.497
Difficulty in abstract thinking	2.50 (0.99)	3.19 (1.42)	0.108
Lack of spontaneity and flow of conversation	2.50 (1.15)	3.12 (1.59)	0.194
Stereotyped thinking	2.61 (0.92)	3.06 (1.29)	0.244
PANSS general	38.75 (5.27)	43.10 (12.92)	0.171
Somatic concern	2.44 (1.20)	2.62 (0.96)	0.634
Anxiety	2.61 (0.92)	3.31 (1.30)	0.076
Guilt feelings	1.67 (0.69)	2.38 (0.96)	0.018*
Tension	2.44 (0.78)	2.93 (1.29)	0.182
Mannerisms and posturing	2.67 (0.84)	2.93 (1.57)	0.528
Depression	2.23 (0.67)	2.69 (0.87)	0.132
Motor retardation	2.22 (1.11)	2.56 (1.21)	0.400
Uncooperativeness	1.56 (0.86)	2.19 (1.47)	0.130
Unusual thought content	3.11 (1.13)	3.00 (1.32)	0.793
Disorientation	1.93 (0.79)	2.31 (1.45)	0.232
Poor attention	2.89 (0.83)	3.19 (1.64)	0.501
Lack of judgment and insight	2.83 (0.79)	2.93 (1.73)	0.819
Disturbance of volition	2.44 (1.10)	2.88 (1.15)	0.272
Poor impulse control	2.44 (0.92)	2.75 (1.34)	0.440
Preoccupation	2.17 (0.86)	2.62 (0.96)	0.151
Active social avoidance	2.94 (1.21)	3.19 (1.47)	0.601

For high definition images please see annex

3.3 Cognitive behavioral assessments:

We found significant differences between NC and SZ groups in terms of years of education and cognitive performance (Table 6).

Table 6. Cognitive behavioral assessments in schizophrenia patients and normal controls

	NC		SZ		P value df=77
	Mean	**SD**	**Mean**	**SD**	
Block design from WAIS-III	12.03	3.289	9.12	3.198	0.001
Similitudes from WAIS-III	11.36	2.653	7.27	2.293	0.001
Vocabulary from WAIS-III	10.44	2.259	6.24	2.465	0.001
Raven percentile	80.56	18.320	50.99	24.827	0.001
Years of education	18.41	3.88	11.72	2.87	0.001

For high definition images please see annex

Discussion

The main purpose of the present study was to investigate the relation between schizophrenia symptoms and gray and white matter densities and the effect of sex-specific differences on this relationship and the effect of (partialling for) gender on these relationships.

As hypothesized schizophrenia patients showed several GMD and WMD abnormalities compared to normal controls. In addition, males with schizophrenia showed lower GMD compared to same-sex normal controls, while no such differences were observed in the corresponding contrast for females.

Structural findings

Schizophrenia patients had lower GMD in the anterior cingulate cortex, left middle temporal cortex in comparison to normal controls. These findings are consistent with the literature in patients with schizophrenia (Kong et al., 2014), specifically the decreased GMD in the left middle temporal cortex (Brosch et al., 2022; Kong et al., 2014). The anterior cingulate finding is of particular interest. A

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

study showed that “at risk” subjects who actually develop psychosis had significantly smaller anterior cingulate volumes (Dazzan et al., 2012). Furthermore, in a meta-analysis by Sepede and colleagues (2014) argued that alterations of the anterior cingulate cortex seemed to be more common in schizophrenia than in bipolar disorder. On the other hand, patients had higher GMD in the left posterior cingulate compared to normal controls. The increased GMD of the posterior cingulate in schizophrenia patients may indicate a compensatory mechanism in response to the anterior cingulate deficit (Andreasen et al. 1990). Newell et al., (2006) have found increased cannabinoid receptor density in the posterior cingulate cortex in schizophrenia. This finding was not correlated to cannabinoid use, which is similar to patients in our study who had no active drug use. This region seems to be more preserved in the early stages of illness as shown in some studies where no differences in bilateral posterior cingulate gyrus in early episode patients were found, despite the presence of significant gray matter reductions in several other brain regions as parahippocampal, frontal, and temporal regions (Ellison-Wright et al., 2008).

Correlations with positive and negative symptoms

The analyses revealed several correlations between symptoms and GMD in schizophrenia patients regardless of sex: between positive symptoms and GMD in the left insula and right caudate; between negative symptoms and GMD in the right middle frontal cortex and the posterior lobe of right cerebellum (uvula). We observed inverse correlation between positive symptoms scores and GMD in the right parietal (precuneus), the posterior lobe of left cerebellum (uvula) and between negative symptoms and GMD in the anterior lobe of the left cerebellum. We also observed correlation between WMD and symptoms: between positive symptoms and WMD in the right middle frontal region and between negative symptoms and WMD in the right superior frontal region. We observed inverse correlation between positive symptoms and WMD in both right inferior occipital and right occipital cuneus regions. Additionally, patients showed inverse correlations between negative symptoms and WMD in the left superior frontal region. We found individual symptoms such as conceptual disorganization to be correlate with both GMD and WMD. We observed inverse correlations between lack of spontaneity and hallucinations and GMD. Hostility and grandiosity inversely correlated with WMD.

Our significant finding of the positive relationship between positive symptoms and in the insula and the caudate GMD is also consistent with some previous studies. The insula is situated at the interface of frontal, parietal and temporal lobes. It is involved in cognitive, emotional, and somato-sensorial processes and provides a hub that integrates salient stimuli with somatosensory and

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

autonomic information (Supekar et al., 2012) and has been involved in emotional interoceptive representations (Gasquoine, 2014) and positive symptoms were shown to correlate with reward anticipation signal in the insula in individuals at high risk to develop psychosis (Wotruba et al., 2014). A previous study by Rolland et al., (2015) demonstrated that patients with acoustico-verbal hallucinations show bilaterally greater resting state functional connectivity in the insula. Similarly, Sepede and colleagues (2014) demonstrated that significantly altered functioning of the insula in schizophrenia, and proposed it as a candidate trait marker for psychosis (Sepede et al., 2014). We postulate that due to its location at the interface of frontal, parietal and temporal lobes, the insula is involved in cognitive, emotional, and somato-sensorial processes, hence providing a hub that integrates salient stimuli with somatosensory and autonomic information (Supekar et al., 2012). The increased GMD could be associated with the over stimulation of cognitive, emotional and somato-sensorial processes regulated by the insula resulting in delusions and hallucinations, which are characterized by amplification of emotional and sensory motor perception and processing. There is a strong functional connectivity between the insula and caudate and the caudate is implicated emotive and cognitive regions including the amygdala and portions of the anterior and posterior cingulate and has been involved in the neurobiology of schizophrenia positive symptoms in relation to dopamine dysfunction (P. Seeman, 2013), although caudate abnormalities may be related to medication exposure (Wotruba, et al., 2014).

Another interesting finding was our result that GMD in the parietal cortex was inversely correlated with the positive symptoms. Several studies show that positive symptoms were related to deficits of logical reasoning processes (Langdon et al., 2010). Such processes are mediated by the parietal cortex (Wendelken, 2014). For example, Hinton et al (2014), found that patients with depression who had reasoning deficits showed lower activations in the parietal cortex. In accordance with these results Dazzan and colleagues (2012), found that subjects who eventually developed schizophrenia had smaller volumes in the parietal cortex.

Of particular interest were the positive correlations in the GMD in the middle frontal and WMD of the superior frontal with negative symptoms. These findings are similar to those of Nesvag et al (2009) who demonstrated that the severity of negative symptoms was mainly related to larger gray matter volumes of the frontal lobe (Nesvag et al., 2009). Several studies point out at the importance of this region in emotion regulation, and in down-regulation of emotional processing (Golkar et al., 2012) in normal population. Negative symptoms have been attributed to overinhibition of affective processes and maladaptive cognitive emotion regulation

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

strategies (O'Driscoll et al., 2014). These processes were associated with increased frontal activation and volume (Nesvag et al., 2009), while disinhibition and emotional lability have been associated with frontal lesions (Bonelli et al., 2007). For example, Smith et al., (2013) showings that a decrease in volume of the dorsolateral frontal cortex (DLPFC) is associated with improvement of depression symptoms in patients with depression. WM connectivity abnormalities in the superior frontal executive region have been proposed to explain negative symptoms in schizophrenia (Asami et al., 2014; Fuentes et al., 2022). In accordance with these results, a study by Dazzan and colleagues (2012), demonstrated that subjects who develop affective psychosis had reductions in the frontal cortex (Dazzan et al., 2012). A meta-analysis by Kohn et al. (2014) concludes that the middle frontal region (DLPFC) plays a key role in action inhibition and proposes that it modulates “higher order ‘cold’ regulatory processes”. In view of these findings, it would be reasonable to say that negative symptoms that share several characteristic of depression are associated with over-engagement of the frontal cortex in affective inhibitory processes in schizophrenia patients.

Present findings point to the importance of the cerebellum in mediation of positive and negative symptoms in the brain. Historically, the cerebellum was largely ignored in schizophrenia research. In 1979, Heath and colleagues were among the first groups to pinpoint gross pathology of the cerebellum in psychotic patients (Heath et al., 1979). In 1995, Martin and Albers concluded that morphological and functional data support the role of the cerebellar dysfunction in the pathogenesis of schizophrenia (Martin et al., 1995). In their review, Andreasen & Pierson (2008) argued that the cerebellum plays a role in higher cognitive and emotional functions. The cerebellum with its cortical connections (the limbic system, the frontal, parietal, prefrontal, occipital, and temporal cortex) opens a pathway for explaining the diversity of schizophrenia symptoms (Andreasen et al., 1988). Based on our results, the cerebellum was mainly correlated with the negative symptoms. In their review, Stoodley et al. (2010) specified that the posterior cerebellum was linked to cognition and the posterior vermis with emotion and cognitive affective syndromes such as passivity, blunted affect and withdrawal. This may be in agreement with previous research findings considering the cerebellum as an emotional pacemaker (Stoodley et al., 2010). Our results point out to the involvement of the vermis (affective) and the posterior cerebellum (cognitive) in regulation of negative symptoms such that increased cognitive regulation/inhibition is associated with decreased emotional processes which may play a role in negative symptoms. The negative relation between the cognitive part of the cerebellum and positive symptoms is intriguing. Symptoms such as hallucinations and delusions were found to be

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

associated with deficits in several cognitive processes (Laroi et al., 2007), perception and correction errors (Allen et al., 2004), source and self-monitoring (Seal et al., 2004), stimulus recognition (Tracy et al., 2013), and reality monitoring (Sugimori et al., 2014). The relation between these cognitive processes and the cerebellum are not fully understood. It has been reported that a structural deficit in the cerebellum may be involved in disorganization in schizophrenia, which consequently may relate to cognitive dysfunction (Suazo et al., 2014).

Correlations with individual symptoms

In our study, total GMD was inversely correlated with hallucinations, in concordance with several studies showing a similar association with gray matter in the left superior temporal gyrus (Garcia-Marti et al., 2008; Gaser et al., 2004; Neckelmann et al., 2006), left thalamus, and left and right cerebellum (Neckelmann et al., 2006) middle/inferior right prefrontal gyri (Gaser et al., 2004), bilateral insula and left amygdala (Garcia-Marti et al., 2008).

Here we report for the first time the relation between total WMD and hostility, where increased WMD is correlated with less hostility. Only two related studies by Hoptman et al., (2002, 2010) have found white matter microstructure abnormalities of the inferior frontal, in particular higher trace, i.e. the average diffusion coefficient of white matter tracts over 3D directions. The authors also found reduced functional connectivity in white matter between the amygdala and ventral prefrontal cortex regions to be correlated with increased aggression in patients with schizophrenia (Hoptman et al., 2010; Hoptman et al., 2002). More recently, findings show a relation between altered white matter connectivity in the cingulum and aggression in schizophrenia, (He et al. 2021) and in the visuospatial network (An et al., 2021). Of particular interest is the association between greater WMD and more severe symptom scores of conceptual disorganization and attention deficits. To our knowledge, no other study has reported such findings in schizophrenia. To make sense of this finding, we seek support from other psychopathologies. Similar findings have been reported in autism, where increased white matter volume was associated with language and communication deficits (Herbert et al., 2004), which are fundamental elements in the construction of conceptual disorganization. However, further studies are needed in schizophrenia to support this view.

The abnormalities in GMD and WMD in our group of schizophrenia patients in comparison to normal controls were not in the same regions that correlated with schizophrenia clinical symptoms as measured by the PANSS. This is relevant and we postulate that cognitive deficits play a role in such discrepancy. We reviewed neuropsychological cognitive data collected

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

(the WAIS-III and Raven percentile tests) from the patients and normal controls. Significant deficits were observed in the schizophrenia groups in all measures when compared to normal controls (Table 6). Abnormalities in the left middle temporal, the left inferior frontal and the left posterior parietal regions were found to be correlated with deficits in emotional memory accuracy in another study performed by our group (Lakis et al., 2011), and several studies have shown abnormalities is these regions in relation with deficits in mental rotation abilities (Mazhari et al., 2014), and language processing (Tagamets et al., 2014).

Behavioral findings

Schizophrenia patients showed significant deficits in all neuropsychological measures when compared to normal controls subjects. This is consistent with numerous previous reports (Brebion et al., 2013).

Sex specific structural differences

Male patients had decreased total GMD relative to same-sex controls, but we observed no differences between female groups. These findings may reflect a more defused and generalized cortical loss in males. In comparison, females might compensate by preserving cortical densities in other cerebral regions. For example, Abbs et al, (2011), found that females with schizophrenia showed decreases in anterior cingulate volume that were compensated in the inferior parietal lobe. Relatively normalized parietal volumes correlated with preservation of verbal memory processing (Abbs et al., 2011). This task correlated with the anterior cingulate volumes in same-sex normal controls. Male patients seem to present less structural compensation. A review by Salem and Kring (1998) attribute structural and neural lack of compensation in male patients to several factors, including: a) the central nervous system in males takes longer time to develop and thus the risk to neurological insults is higher (Geschwind et al., 1985; Salem et al., 1998) b) there is a greater hemispheric lateralization in males, thus damage to one hemisphere at early stages of development are more difficult to compensate; c) there is overall presence of more prenatal abnormalities of neuronal migration in males relative to females (Geschwind et al., 1985). Findings by Niu et al, (2004) support these theories. They found a significant left-smaller-than-right volumetric asymmetry of the amygdala in male patients with schizophrenia. In addition, male patients had reduced volumes in the bilateral amygdala while female patients had reductions only in right amygdala compared to same-sex controls (Niu et al., 2004). Several studies show that male have more GM abnormalities than females with schizophrenia: these include reduced prefrontal volumes, reduced anterior temporal horn and medial temporal lobe volumes, more specifically amygdala, hippocampus, superior temporal and larger ventricular-brain ratios (VBR) or that females

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

have more preserved cerebral morphology (Andreason et al., 1990; Gur et al., 2000). Several authors have suggested that these differences are due to the neuroprotective effects of estrogen in females (Allen et al., 2013). The lack of differences in white matter densities between males with schizophrenia and same-sex controls was of particular interest. Findings show that abnormalities in white matter in patients with schizophrenia are related disturbed sexual dimorphism rather than decreased white matter densities (Savadjiev et al., 2014).

Sex specific correlations

Females with schizophrenia showed no correlations between brain densities and symptoms, while male patients showed several correlations, specifically between WMD and conceptual disorientation, and between both GMD and WMD and attention deficits. In addition, inverse correlation were observed between WMD and ideas of grandiosity.

In our study, the negative correlation between WMD and ideas of grandiosity observed in males with schizophrenia remained significant after grouping male and female patients together. Thus, significant results in schizophrenia research might be biased and related to only males but not females and vice versa giving support to the important role of sex differences in schizophrenia. To our knowledge, this is the first study to report a direct relation between white matter density and these symptoms and the related sex difference. Interestingly a study by Sallet et al., (2003) found correlations between cortical gyrification index and grandiosity (Sallet et al., 2003) and more recently increased structural connectivity of the supero-lateral medial forebrain bundle was reported to correlate with paranoid ideation and grandiosity (Bracht et al., 2019). Gyrification index is a marker of degree of cortical folding which is hypothesized to represent underlying white matter volume (Armstrong et al., 1995). Sex difference in functional connectivity has been reported in patients with schizophrenia. Lei et al (2015), found that male and female patients have disturbed functional integration in two separate networks: the sensorimotor network and the default mode network. The authors suggest that sex-specific patterns of functional aberration existed in schizophrenia, and these patterns were associated with the clinical features both in male and female patients. The white matter abnormalities are in support of neurodevelopmental disturbance that is more evident in males than females with schizophrenia.

Of particular interest is that female patients in our study had relatively worse symptoms scores compared to male patients, but it was males who exhibited more diffuse GMD and WMD abnormalities. In addition, females with schizophrenia had no association between total GMD, WMD, CSF, or total brain volume with any of the individual schizophrenia

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

symptoms. Only males with schizophrenia showed an inverse correlation between ideas of grandiosity and WMD. Additionally, were observed correlations between disorientation and WMD and attention deficits and GMD and WMD only in males with schizophrenia. To our knowledge, this is the first study to report such finding only in males with schizophrenia. Savadjiev et al., (2014) found that disturbances of normal sexual dimorphism in white matter were correlated with the degree of negative symptoms. The authors demonstrated negative symptom strength increased with the reduction in connection asymmetry in males with schizophrenia, while stronger negative symptoms were correlated with increase in asymmetry in females with schizophrenia. Correlation between increased WMD and attention deficits has been reported in patients with ADHD (Batty et al., 2010). Studies show that males with schizophrenia show more attention deficits compared to female patients (Seidman et al., 1997). These findings suggest that females with schizophrenia may be less vulnerable to particular cognitive deficits compared to males with schizophrenia (Goldstein et al., 1998).

In support of our findings is that females with schizophrenia tend to present less ideas of grandiosity in comparison with males with schizophrenia. A study on psychotic experiences in adolescence found that boys reported more grandiosity and anhedonia and had more parent-rated negative symptoms than girls (Ronald et al., 2014). Furthermore, prevalence of grandiosity was reported to be higher in males than females with early episode psychosis (Wigman et al., 2011). These findings support that males with schizophrenia seem to have a greater biological vulnerability to worse symptoms, consequent social disability in the face of psychosis and poorer prognosis, while females have either a biological or a psychosocial resilience to the illness (Ring et al., 1991).

Sex specific behavioral findings

Sex differences emerged in patients with schizophrenia, where normal control males significantly outperformed male patients on all subcategories of the WAIS-III and Raven percentile tests, while female patients showed fewer deficits when compared to same-sex controls, such that we found no differences between female groups on the block design task. When we performed direct comparisons between females and males with schizophrenia, females outperformed males on the Raven percentile task. These findings are of particular interest since both these tasks test visual and perceptive reasoning. These findings are consistent with studies by our groups showing no differences between female schizophrenia patients and female controls during mental rotation tasks, while male patient had worse performance on the same task compared to the same-sex controls (Jimenez et al., 2010). Studies on healthy

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

population show better performances in males compared to females on spacio-visual tasks (Astor, 1998). Together these findings support the presence of an inverse sexual dimorphism in schizophrenia patients (Mendrek, 2007; Luckhoff et al., 2022). Sex differences observed support existing literature showing males with schizophrenia have worse cognitive performance compared to females with schizophrenia. Female schizophrenia have preserved language, verbal memory and visuospatial memory and have better performances in processing speed and episodic memory compared to males with schizophrenia (Goldstein et al., 1998).

Exploratory analyses

Irrelevant of sex of patients our exploratory prediction model of the linear regression relationship between GMD and WMD with the PANSS symptoms score has produced interesting results.

Increased hostility and grandiosity symptoms in our patients predicted decreased WMD. Several studies showed that reduced functional connectivity in white matter between the amygdala and ventral prefrontal cortex regions has been associated with increased aggression in patients with schizophrenia (Hoptman et al., 2010; Hoptman et al., 2002). Interestingly, we report for the first time that the intensity of conceptual disorganization was a predicting factor of increased GMD and WMD in schizophrenia patients in our study. Similar findings have been reported in autism, where increased white matter volume was associated with language and communication deficits (Herbert et al., 2004), which are fundamental elements in the construction of conceptual disorganization, however further studies are needed in schizophrenia to support this view. In addition, the intensity of lack of spontaneity and hallucination symptoms predicted the degree of GMD loss. This is in concordance with several studies showing a similar association with gray matter in the left superior temporal gyrus (Garcia-Marti et al., 2008; Gaser et al., 2004; Neckelmann et al., 2006), left thalamus, and left and right cerebellum (Neckelmann et al., 2006) middle/inferior right prefrontal gyri (Gaser et al., 2004), bilateral insula and left amygdala (Garcia-Marti et al., 2008).

Conclusion

Our results shed further light on the neuroanatomical underpinnings of psychosis, providing insights into the physiological nature of positive versus negative symptoms. In essence, our study provides neurobiological evidence on the validity of a combination of overlapping and differing brain structural neuropsychopathology assessed by the PANSS. More importantly, our results reject the notion that all patients might share a core network of neuropathology, because the

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

different symptoms correlated with different structural findings, and could be independent of each other. To this end, future studies should investigate the correlation between individual symptoms and specific cerebral regions.

We should note that despite significant findings in this domain, neuroanatomical abnormalities are insufficiently sensitive to be individually or collectively diagnostic of the disease (or its prognosis/etiology). Hence, the abnormalities have yet to be integrated into a clinically validated model, which would permit a coherent approach towards early detection, prevention, and treatments.

Considerable heterogeneity remains across studies investigating changes in GM and WM structures in schizophrenia. Despite the diligent efforts to control for age, sex, medications, and disease onset, heterogeneous symptoms could contribute to inconsistent findings. Our group previously advocated that future studies should group large number of patients by symptom dimensions. (Fahim et al., 2005; Stip et al., 2005). Taking into account the importance of sex differences in schizophrenia, studies using the symptoms' dimensional approach in schizophrenia may be important for elucidating the core pathophysiology of this illness.

Limitation

We should consider the limitations of the present study such as potential effects of antipsychotic medication (past and current). We specify that all our patients were receiving consistent doses of first- or second-generation antipsychotic medication. All patients were in a stable phase of their illness (defined as no relapse within the last two months and no change in their antipsychotic treatment within the last month). All patients received at least one atypical antipsychotic (chlorpromazine equivalence was calculated) (Woods, 2003). The second limitation is that our clinical assessment was not exhaustive. We used only one scale to assess the positive and negative symptoms (i.e., the PANSS). Hence, we anticipate in our future research to investigate the association of the regions within each of the positive and negative symptoms using further scales.

Acknowledgement

We thank the subjects who participated in this study. The Canadian Institutes of Health Research (CIHR) and The Institute of Gender and Health (IGH) funded this study. The first author is the holder of the Fond de recherche en santé du Québec (FRSQ) fellowship. Adrianna Mendrek is an FRQS (Fonds de recherche en santé du Québec) Junior II Research Scholar.

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

The authors would like to thank Josiane Bourque and Drs. Tania Pampoulova, Ait Bentaleb and Pierre Lalonde for their valuable reference of patients in this project. All authors have no financial, personal, or other potential conflict of interest to disclose.

References

Abbs, B., Liang, L., Makris, N., Tsuang, M., Seidman, L. J., & Goldstein, J. M. (2011). Covariance modeling of MRI brain volumes in memory circuitry in schizophrenia: Sex differences are critical. *NeuroImage, 56*(4), 1865-1874. https://doi.org/10.1016/j.neuroimage.2011.03.079

Allen, D. N., Strauss, G. P., Barchard, K. A., Vertinski, M., Carpenter, W. T., & Buchanan, R. W. (2013). Differences in developmental changes in academic and social premorbid adjustment between males and females with schizophrenia. *Schizophrenia research, 146*(1-3), 132-137.

Alemán-Gómez, Y., Najdenovska, E., Roine, T., Fartaria, M. J., Canales-Rodríguez, E. J., Rovó, Z., Hagmann, P., Conus, P., Do, K. Q., Klauser, P., Steullet, P., Baumann, P. S., & Bach Cuadra, M. (2020). Partial-volume modeling reveals reduced gray matter in specific thalamic nuclei early in the time course of psychosis and chronic schizophrenia. *Human brain mapping*, *41*(14), 4041–4061. https://doi.org/10.1002/hbm.25108

Allen, P. P., Johns, L. C., Fu, C. H., Broome, M. R., Vythelingum, G. N., & McGuire, P. K. (2004). Misattribution of external speech in patients with hallucinations and delusions. *Schizophrenia research, 69*(2-3), 277-287. https://doi.org/10.1016/j.schres.2013.01.032

An, I., Choi, T. K., Bang, M., & Lee, S. H. (2021). White Matter Correlates of Hostility and Aggression in the Visuospatial Function Network in Patients With Schizophrenia. *Frontiers in psychiatry*, *12*, 734488. https://doi.org/10.3389/fpsyt.2021.734488

American Psychiatric Association (Ed.). (2000). *Diagnostic and statistical manual of mental disorders (4th ed., text rev.)*: Washington, DC.

Andreasen, N. C., Ehrhardt, J. C., Swayze, V. W., 2nd, Alliger, R. J., Yuh, W. T., Cohen, G., et al. (1990). Magnetic resonance imaging of the brain in schizophrenia. The pathophysiologic significance of structural abnormalities. *Archives of general psychiatry, 47*(1), 35-44.

Andreasen, N. C., Flaum, M., Swayze, V. W., 2nd, Tyrrell, G., & Arndt, S. (1990). Positive and negative symptoms in schizophrenia. A critical reappraisal. *Archives of general psychiatry, 47*(7), 615-621. https://doi.org/10.1001/archpsyc.1990.01810190015002

Andreasen, N. C., & Pierson, R. (2008). The role of the cerebellum in schizophrenia. *Biological psychiatry, 64*(2), 81-88.

Andreasen, N. C., Shore, D., Burke, J. D., Jr., Grove, W. M., Lieberman, J. A., Oltmanns, T. F., et al. (1988). Clinical phenomenology. *Schizophrenia bulletin, 14*(3), 345-363. https://doi.org/10.1093/schbul/14.3.345

Armstrong, E., Schleicher, A., Omran, H., Curtis, M., & Zilles, K. (1995). The ontogeny of human gyrification. *Cerebral cortex, 5*(1), 56-63.

Asami, T., Hyuk Lee, S., Bouix, S., Rathi, Y., Whitford, T. J., Niznikiewicz, M., et al. (2014). Cerebral white matter abnormalities and their associations with negative but not positive symptoms of schizophrenia. *Psychiatry research, 222*(1-2), 52-59. https://doi.org/10.1016/j.pscychresns.2014.02.007

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage, 38*(1), 95-113. https://doi.org/10.1016/j.neuroimage.2007.07.007

Ashburner, J., & Friston, K. J. (2001). Why voxel-based morphometry should be used. *NeuroImage, 14*(6), 1238-1243. https://doi.org/10.1006/nimg.2001.0961

Ashburner, J., & Friston, K. J. (2009). Computing average shaped tissue probability templates. *NeuroImage, 45*(2), 333-341. https://doi.org/10.1016/j.neuroimage.2008.12.008

Astor, R. S., Ortiz, M.L., Sutherland, R.J. . (1998). A characterization of performance by men and women in a virtual Morris water task: A large and reliable sex difference. *Behavioural Brain Research, 93* 185-190. https://doi.org/10.1016/s0166-4328(98)00019-9

Batty, M. J., Liddle, E. B., Pitiot, A., Toro, R., Groom, M. J., Scerif, G., et al. (2010). Cortical gray matter in attention-deficit/hyperactivity disorder: a structural magnetic resonance imaging study. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(3), 229-238. https://doi.org/10.1016/j.jaac.2009.11.008

Bonelli, R. M., & Cummings, J. L. (2007). Frontal-subcortical circuitry and behavior. *Dialogues in clinical neuroscience, 9*(2), 141-151. https://doi.org/10.31887/DCNS.2007.9.2/rbonelli

Bracht, T., Viher, P. V., Stegmayer, K., Strik, W., Federspiel, A., Wiest, R., & Walther, S. (2019). Increased structural connectivity of the medial forebrain bundle in schizophrenia spectrum disorders is associated with delusions of paranoid threat and grandiosity. *NeuroImage. Clinical*, *24*, 102044. https://doi.org/10.1016/j.nicl.2019.102044

Brebion, G., Villalta-Gil, V., Autonell, J., Cervilla, J., Dolz, M., Foix, A., et al. (2013). Cognitive correlates of verbal memory and verbal fluency in schizophrenia, and differential effects of various clinical symptoms between male and female patients. *Schizophrenia research, 147*(1), 81-85. https://doi.org/10.1016/j.schres.2013.03.014

Brosch, K., Stein, F., Schmitt, S., Pfarr, J. K., Ringwald, K. G., Thomas-Odenthal, F., Meller, T., Steinsträter, O., Waltemate, L., Lemke, H., Meinert, S., Winter, A., Breuer, F., Thiel, K., Grotegerd, D., Hahn, T., Jansen, A., Dannlowski, U., Krug, A., Nenadić, I Kircher, T. (2022). Reduced hippocampal gray matter volume is a common feature of patients with major depression, bipolar disorder, and schizophrenia spectrum disorders. *Molecular psychiatry*, 10.1038/s41380-022-01687-4. Advance online publication. https://doi.org/10.1038/s41380-022-01687-4

Chang, W. C., Hui, C. L., Tang, J. Y., Wong, G. H., Lam, M. M., Chan, S. K., et al. (2011). Persistent negative symptoms in first-episode https://doi.org/10.1016/j.schres.2011.09.006 Choi, J. S., Chon, M. W., Kang, D. H., Jung, M. H., & Kwon, J. S. (2009). Gender difference in the prodromal symptoms of

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

first-episode schizophrenia. *Journal of Korean medical science, 24*(6), 1083-1088. https://doi.org/10.3346/jkms.2009.24.6.1083

Dazzan, P., Soulsby, B., Mechelli, A., Wood, S. J., Velakoulis, D., Phillips, L. J., et al. (2012). Volumetric abnormalities predating the onset of schizophrenia and affective psychoses: an MRI study in subjects at ultrahigh risk of psychosis. *Schizophrenia bulletin, 38*(5), 1083-1091. https://doi.org/10.1093/schbul/sbr035

Eickhoff S, Walters NB, Schleicher A, Kril J, Egan GF, Zilles K, Watson JD, Amunts K. High-resolution MRI reflects myeloarchitecture and cytoarchitecture of human cerebral cortex. Hum Brain Mapp. 2005 Mar;24(3):206-15. doi: 10.1002/hbm.20082.

Ellison-Wright, I., Glahn, D. C., Laird, A. R., Thelen, S. M., & Bullmore, E. (2008). The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis. *The American journal of psychiatry, 165*(8), 1015-1023. https://doi.org/10.1176/appi.ajp.2008.07101562

Fahim, C., Stip, E., Mancini-Marie, A., Mensour, B., Boulay, L. J., Leroux, J. M., et al. (2005). Brain activity during emotionally negative pictures in schizophrenia with and without flat affect: an fMRI study. *Psychiatry Res, 140*(1), 1-15. https://doi.org/10.1016/j.pscychresns.2005.06.003

Fuentes-Claramonte, P., Ramiro, N., Torres, L., Argila-Plaza, I., Salgado-Pineda, P., Soler-Vidal, J., García-León, M. Á., Albacete, A., Bosque, C., Panicalli, F., Boix, E., Munuera, J., Tristany, J., Sarró, S., Bernardo, M., Salvador, R., McKenna, P. J., & Pomarol-Clotet, E. (2022). Negative schizophrenic symptoms as prefrontal cortex dysfunction: Examination using a task measuring goal neglect. *NeuroImage. Clinical*, *35*, 103119. https://doi.org/10.1016/j.nicl.2022.103119

Garcia-Marti, G., Aguilar, E. J., Lull, J. J., Marti-Bonmati, L., Escarti, M. J., Manjon, J. V., et al. (2008). Schizophrenia with auditory hallucinations: a voxel-based morphometry study. *Progress in neuro-psychopharmacology & biological psychiatry, 32*(1), 72-80. https://doi.org/10.1016/j.pnpbp.2007.07.014

Gaser, C., Nenadic, I., Volz, H. P., Buchel, C., & Sauer, H. (2004). Neuroanatomy of "hearing voices": a frontotemporal brain structural abnormality associated with auditory hallucinations in schizophrenia. *Cerebral cortex, 14*(1), 91-96. https://doi.org/10.1093/cercor/bhg107

Geschwind, N., & Galaburda, A. M. (1985). Cerebral lateralization. Biological mechanisms, associations, and pathology: I. A hypothesis and a program for research. *Archives of neurology, 42*(5), 428-459. https://doi.org/10.1001/archneur.1985.04060050026008

Gasquoine P. G. (2014). Contributions of the insula to cognition and emotion. *Neuropsychology review*, *24*(2), 77–87. https://doi.org/10.1007/s11065-014-9246-9

Goldstein, J. M., Seidman, L. J., Goodman, J. M., Koren, D., Lee, H., Weintraub, S., et al. (1998). Are there sex differences in neuropsychological functions among patients with schizophrenia? *The American journal of psychiatry, 155*(10), 1358-1364. https://doi.org/10.1176/ajp.155.10.1358

Golkar, A., Lonsdorf, T. B., Olsson, A., Lindstrom, K. M., Berrebi, J., Fransson, P., et al. (2012). Distinct contributions of the dorsolateral prefrontal and orbitofrontal cortex during emotion regulation. *PloS one, 7*(11), e48107. https://doi.org/10.1371/journal.pone.0048107

Gur, R. E., Cowell, P. E., Latshaw, A., Turetsky, B. I., Grossman, R. I., Arnold, S. E., et al. (2000). Reduced dorsal and orbital prefrontal gray matter volumes in schizophrenia. *Archives of general psychiatry, 57*(8), 761-768. https://doi.org/10.1001/archpsyc.57.8.761

He, Y., Li, K., Li, J., Wang, J., Cheng, N., Xiao, J., & Jiang, T. (2021). Cingulum White Matter Integrity as a Mediator Between Harm Avoidance and Hostility. *Neuroscience*, *461*,36–43. https://doi.org/10.1016/j.neuroscience.2021.02.031

Heath, R. G., Franklin, D. E., & Shraberg, D. (1979). Gross pathology of the cerebellum in patients diagnosed and treated as functional psychiatric disorders. *The Journal of nervous and mental disease, 167*(10), 585-592. https://doi.org/10.1097/00005053-197910000-00001

Herbert, M. R., Ziegler, D. A., Makris, N., Filipek, P. A., Kemper, T. L., Normandin, J. J., et al. (2004). Localization of white matter volume increase in autism and developmental language disorder. *Annals of neurology, 55*(4), 530-540. https://doi.org/10.1002/ana.20032

Hinton, E. C., Wise, R. G., Singh, K. D., & von Hecker, U. (2014). Reasoning with linear orders: differential parietal cortex activation in sub-clinical depression. An FMRI investigation in sub-clinical depression and controls. *Frontiers in human neuroscience, 8*, 1061. https://doi.org/10.3389/fnhum.2014.01061

Hoptman, M. J., D'Angelo, D., Catalano, D., Mauro, C. J., Shehzad, Z. E., Kelly, A. M., et al. (2010). Amygdalofrontal functional disconnectivity and aggression in schizophrenia. *Schizophrenia bulletin, 36*(5), 1020-1028. https://doi.org/10.1093/schbul/sbp012

Hoptman, M. J., Volavka, J., Johnson, G., Weiss, E., Bilder, R. M., & Lim, K. O. (2002). Frontal white matter microstructure, aggression, and impulsivity in men with schizophrenia: a preliminary study. *Biological psychiatry, 52*(1), 9-14. https://doi.org/10.1016/s0006-3223(02)01311-2

Hurvich, C. M., & Tsai, C. L. (1995). Model selection for extended quasi-likelihood models in small samples. *Biometrics, 51*(3), 1077-1084.

Jablensky, A. (2006). Subtyping schizophrenia: implications for genetic research. *Molecular psychiatry, 11*(9), 815-836. https://doi.org/10.1038/sj.mp.4001857

Jablensky, A. (2010). The diagnostic concept of schizophrenia: its history, evolution, and future prospects. *Dialogues in clinical neuroscience, 12*(3), 271-287. https://doi.org/10.31887/DCNS.2010.12.3/ajablensky

Jimenez, J. A., Mancini-Marie, A., Lakis, N., Rinaldi, M., & Mendrek, A. (2010). Disturbed sexual dimorphism of brain activation during mental rotation in schizophrenia. *Schizophrenia research, 122*(1-3), 53-62. https://doi.org/10.1016/j.schres.2010.03.011

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia bulletin, 13*(2), 261-276. https://doi.org/10.1093/schbul/13.2.261

Kohn, N., Eickhoff, S. B., Scheller, M., Laird, A. R., Fox, P. T., & Habel, U. (2014). Neural network of cognitive emotion regulation--an ALE meta-analysis and MACM analysis. *NeuroImage, 87*, 345-355. https://doi.org/10.1016/j.neuroimage.2013.11.001

Kong, L., Herold, C. J., Zollner, F., Salat, D. H., Lasser, M. M., Schmid, L. A., et al. (2014). Comparison of grey matter

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

volume and thickness for analysing cortical changes in chronic schizophrenia: A matter of surface area, grey/white matter intensity contrast, and curvature. *Psychiatry research*.

Kring, A. M., Gur, R. E., Blanchard, J. J., Horan, W. P., & Reise, S. P. (2013). The Clinical Assessment Interview for Negative Symptoms (CAINS): final development and validation. *The American journal of psychiatry, 170*(2), 165-172. https://doi.org/10.1176/appi.ajp.2012.12010109

Lakis, N., Jimenez, J. A., Mancini-Marie, A., Stip, E., Lavoie, M. E., & Mendrek, A. (2011). Neural correlates of emotional recognition memory in schizophrenia: effects of valence and arousal. *Psychiatry research, 194*(3), 245-256. https://doi.org/10.1016/j.pscychresns.2011.05.010

Langdon, R., Ward, P. B., & Coltheart, M. (2010). Reasoning anomalies associated with delusions in schizophrenia. *Schizophrenia bulletin, 36*(2), 321-330. https://doi.org/10.1093/schbul/sbn069

Laroi, F., & Woodward, T. S. (2007). Hallucinations from a cognitive perspective. *Harvard review of psychiatry, 15*(3), 109-117. https://doi.org/10.1080/10673220701401993

Lei, W., Li, M., Deng, W., Zhou, Y., Ma, X., Wang, Q., et al. (2015). Sex-Specific Patterns of Aberrant Brain Function in First-Episode Treatment-Naive Patients with Schizophrenia. *International journal of molecular sciences, 16*(7), 16125-16143. https://doi.org/10.3390/ijms160716125

Luckhoff, H. K., Asmal, L., Scheffler, F., du Plessis, S., Chiliza, B., Smit, R., Phahladira, L., & Emsley, R. (2022). Sex and gender associations with indicators of neurodevelopmental compromise in schizophrenia spectrum disorders. *Schizophrenia research*, *243*, 70–77. https://doi.org/10.1016/j.schres.2022.02.012

Mancevski, B., Keilp, J., Kurzon, M., Berman, R. M., Ortakov, V., Harkavy-Friedman, J., et al. (2007). Lifelong course of positive and negative symptoms in chronically institutionalized patients with schizophrenia. *Psychopathology, 40*(2), 83-92. https://doi.org/10.1159/000098488

Mancini-Marïe, A., Yoon, U., Jiminez, J., Fahim, C., Potvin, S., Grant, J. A., Laverdure-Dupont, D., Dubé, A. A., Betrisey, C., Rainville, P., Evans, A. C., Stip, E., & Mendrek, A. (2018). Sex, Age, Symptoms and Illness Duration and Their Relation with Gyrification Index in Schizophrenia. *Clinical schizophrenia & related psychoses*, *12*(2), 57–68. https://doi.org/10.3371/CSRP.MAYO.070415

Martin, P., & Albers, M. (1995). Cerebellum and schizophrenia: a selective review. *Schizophrenia bulletin, 21*(2), 241-250. https://doi.org/10.1093/schbul/21.2.241

Mazhari, S., & Moghadas Tabrizi, Y. (2014). Abnormalities of mental rotation of hands associated with speed of information processing and executive function in chronic schizophrenic patients. *Psychiatry and clinical neurosciences, 68*(6), 410-417. https://doi.org/10.1111/pcn.12148

Mendrek, A. (2007). Reversal of normal cerebral sexual dimorphism in schizophrenia: evidence and speculations. *Medical hypotheses, 69*(4), 896-902. https://doi.org/10.1016/j.mehy.2007.01.064

Neckelmann, G., Specht, K., Lund, A., Ersland, L., Smievoll, A. I., Neckelmann, D., et al. (2006). Mr morphometry analysis of grey matter volume reduction in schizophrenia: association with hallucinations. *The International journal of neuroscience, 116*(1), 9-23. https://doi.org/10.1080/00207450690962244

Nesvag, R., Saetre, P., Lawyer, G., Jonsson, E. G., & Agartz, I. (2009). The relationship between symptom severity and regional cortical and grey matter volumes in schizophrenia. *Progress in neuro-psychopharmacology & biological psychiatry, 33*(3), 482-490. https://doi.org/10.1016/j.pnpbp.2009.01.013

Newell, K. A., Deng, C., & Huang, X. F. (2006). Increased cannabinoid receptor density in the posterior cingulate cortex in schizophrenia. *Experimental brain research, 172*(4), 556-560.

Niu, L., Matsui, M., Zhou, S. Y., Hagino, H., Takahashi, T., Yoneyama, E., et al. (2004). Volume reduction of the amygdala in patients with schizophrenia: a magnetic resonance imaging study. *Psychiatry research, 132*(1), 41-51. https://doi.org/10.1007/s00221-006-0503-x

O'Driscoll, C., Laing, J., & Mason, O. (2014). Cognitive emotion regulation strategies, alexithymia and dissociation in schizophrenia, a review and meta-analysis. *Clinical psychology review, 34*(6), 482-495. https://doi.org/10.1016/j.cpr.2014.07.002

Ochoa S, Usall J, Cobo J, Labad X, Kulkarni J. Gender differences in schizophrenia and first-episode psychosis: a comprehensive literature review. *Schizophr Res* Treatment. 2012;2012:916198. doi: 10.1155/2012/916198.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*(1), 97-113. https://doi.org/10.1016/0028-3932(71)90067-4

Ring, N., Tantam, D., Montague, L., Newby, D., Black, D., & Morris, J. (1991). Gender differences in the incidence of definite schizophrenia and atypical psychosis--focus on negative symptoms of schizophrenia. *Acta Psychiatr Scand, 84*(6), 489-496. https://doi.org/10.1111/j.1600-0447.1991.tb03182.x

Rolland, B., Amad, A., Poulet, E., Bordet, R., Vignaud, A., Bation, R., Delmaire, C., Thomas, P., Cottencin, O., & Jardri, R. (2015). Resting-state functional connectivity of the nucleus accumbens in auditory and visual hallucinations in schizophrenia. *Schizophrenia bulletin*, *41*(1), 291–299. https://doi.org/10.1093/schbul/sbu097

Salem, J. E., & Kring, A. M. (1998). The role of gender differences in the reduction of etiologic heterogeneity in schizophrenia. *Clinical psychology review, 18*(7), 795-819. https://doi.org/10.1016/s0272-7358(98)00008-7

Sallet, P. C., Elkis, H., Alves, T. M., Oliveira, J. R., Sassi, E., Campi de Castro, C., et al. (2003). Reduced cortical folding in schizophrenia: an MRI morphometric study. *The American journal of psychiatry, 160*(9), 1606-1613. https://doi.org/10.1176/appi.ajp.160.9.1606

Savadjiev, P., Whitford, T. J., Hough, M. E., Clemm von Hohenberg, C., Bouix, S., Westin, C. F., et al. (2014). Sexually dimorphic white matter geometry abnormalities in adolescent onset schizophrenia. *Cerebral cortex, 24*(5), 1389-1396. 1396. https://doi.org/10.1093/cercor/bhs422

Seal, M. L., Aleman, A., & McGuire, P. K. (2004). Compelling imagery, unanticipated speech and deceptive memory: neurocognitive models of auditory verbal hallucinations in schizophrenia. *Cognitive neuropsychiatry, 9*(1-2), 43-72. https://doi.org/10.1080/13546800344000156

Seeman, P. (2013). Schizophrenia and dopamine receptors. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology, 23*(9), 999-1009. https://doi.org/10.1016/j.euroneuro.2013.06.005

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

Seidman, L. J., Goldstein, J. M., Goodman, J. M., Koren, D., Turner, W. M., Faraone, S. V., et al. (1997). Sex differences in olfactory identification and Wisconsin Card Sorting performance in schizophrenia: relationship to attention and verbal ability. *Biological psychiatry, 42*(2), 104-115. https://doi.org/10.1016/S0006-3223(96)00300-9

Sepede, G., Spano, M. C., Lorusso, M., De Berardis, D., Salerno, R. M., Di Giannantonio, M., et al. (2014). Sustained attention in psychosis: Neuroimaging findings. *World journal of radiology, 6*(6), 261-273. https://doi.org/10.4329/wjr.v6.i6.261

Smith, R., Chen, K., Baxter, L., Fort, C., & Lane, R. D. (2013). Antidepressant effects of sertraline associated with volume increases in dorsolateral prefrontal cortex. *Journal of affective disorders, 146*(3), 414-419. https://doi.org/10.1016/j.jad.2012.07.029

Spitzer, R. L., Williams, J. B., Gibbon, M., & First, M. B. (1992). The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. *Archives of general psychiatry, 49*(8), 624-629. https://doi.org/10.1001/archpsyc.1992.01820080032005

Stip, E., Fahim, C., Mancini-Marie, A., Bentaleb, L. A., Mensour, B., Mendrek, A., et al. (2005). Restoration of frontal activation during a treatment with quetiapine: an fMRI study of blunted affect in schizophrenia. *Progress in neuro-psychopharmacology & biological psychiatry, 29*(1), 21-26. https://doi.org/10.1016/j.pnpbp.2004.08.015

Stoodley, C. J., & Schmahmann, J. D. (2010). Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. *Cortex; a journal devoted to the study of the nervous system and behavior, 46*(7), 831-844. https://doi.org/10.1016/j.cortex.2009.11.008

Suazo, V., Diez, A., Montes, C., & Molina, V. (2014). Structural correlates of cognitive deficit and elevated gamma noise power in schizophrenia. *Psychiatry and clinical neurosciences, 68*(3), 206-215. https://doi.org/10.1111/pcn.12120

Sugimori, E., Mitchell, K. J., Raye, C. L., Greene, E. J., & Johnson, M. K. (2014). Brain mechanisms underlying reality monitoring for heard and imagined words. *Psychological science, 25*(2), 403-413. https://doi.org/10.1177/0956797613505776

Supekar, K., & Menon, V. (2012). Developmental maturation of dynamic causal control signals in higher-order cognition: a neurocognitive network model. *PLoS computational biology, 8*(2), e1002374. https://doi.org/10.1371/journal.pcbi.1002374

Tagamets, M. A., Cortes, C. R., Griego, J. A., & Elvevag, B. (2014). Neural correlates of the relationship between discourse coherence and sensory monitoring in schizophrenia. *Cortex; a journal devoted to the study of the nervous system and behavior, 55*, 77-87. https://doi.org/10.1016/j.cortex.2013.06.011

Tracy, D. K., & Shergill, S. S. (2013). Mechanisms Underlying Auditory Hallucinations-Understanding Perception without Stimulus. *Brain sciences, 3*(2), 642-669. https://doi.org/10.3390/brainsci3020642

Wendelken, C. (2014). Meta-analysis: how does posterior parietal cortex contribute to reasoning? *Frontiers in human neuroscience, 8*, 1042. https://doi.org/10.3389/fnhum.2014.01042

Wigman, J. T., Vollebergh, W. A., Raaijmakers, Q. A., Iedema, J., van Dorsselaer, S., Ormel, J., et al. (2011). The structure of the extended psychosis phenotype in early adolescence--a cross-sample replication. *Schizophrenia bulletin, 37*(4), 850-860. https://doi.org/10.1093/schbul/sbp154

Woods, S. W. (2003). Chlorpromazine equivalent doses for the newer atypical antipsychotics. *The Journal of clinical psychiatry, 64*(6), 663-667. https://doi.org/10.4088/jcp.v64n0607

Wotruba, D., Heekeren, K., Michels, L., Buechler, R., Simon, J. J., Theodoridou, A., et al. (2014). Symptom dimensions are associated with reward processing in unmedicated persons at risk for psychosis. *Frontiers in behavioral neuroscience, 8*, 382. https://doi.org/10.3389/fnbeh.2014.00382

Zhao, J., Diao, J., Li, X., Yang, Y., Yao, Y., Shi, S., Yuan, X., Liu, H., & Zhang, K. (2022). Gender Differences in Psychiatric Symptoms and the Social Functioning of 610 Patients with Schizophrenia in Urban China: A 10-Year Follow-Up Study. *Neuropsychiatric disease and treatment*, *18*, 1545–1551. https://doi.org/10.2147/NDT.S373923

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

ANNEX

Table 1. Demographics of schizophrenia patients

	Males Mean (SD)	Females Mean (SD)	P value df=38
Age	31.50 (7.55)	32.65 (6.46)	0.608
Years of education	11.20 (2.06)	12.25 (3.47)	0.253
Age of onset	19.89 (2.97)	24.40 (7.75)	0.007
Duration of illness (years)	11.57 (7.74)	8.25 (5.70)	0.136
Parental socio-educational status	2.82 (.612)	2.62 (1.06)	0.470
Chlorpromazine equivalence	722.50 (383.74)	443.33 (280.94)	0.012

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

Table 2. Regions of gray and white density differences between the schizophrenia group and normal controls based on voxel-based morphometry analyses

	Brain region	K (voxels)	t ($p<0.05$ $P_{FDR-\ corr}$) MNI coordinates
GMD NC > SZ	Anterior cingulate cortex (BA32)	336	6.02 (0, 44, 10)
	Middle temporal cortex (BA21)	373	5.97 (-59, -1, -21)
GMD SZ > NC	Posterior cingulate	230	4.02 (-30, -63, 16)
WMD NC > SZ	Inferior frontal lobe	130	4.12 (-6, 21, -23)
	Posterior parietal lobe	138	3.72 (-9, -48, 66)

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

Table 3. Positive correlations between GMD and WMD regression analysis based on symptoms scores (all results are $p<0.05$, $P_{FWE\text{-}corr}$).

GMD	Region	K	T	MNI
PANSS positive scores	L Insula	523	4.68	-42, -42, 18
	R Caudate	195	4.21	35, -16, -9
PANSS negative scores	R Middle Frontal	467	5.03	38, 36, 42
	R Cerebellum posterior lobe Uvula	206	4.57	39, -84, -21
WMD	**Region**	**K**	**T**	**MNI**
PANSS positive scores	R Middle frontal	240	3.82	27, 57, -8
PANSS negative scores	R superior frontal	72	4.32	14, 56, 24

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

Table 4. Negative correlations between GMD and WMD regression analysis based on symptoms scores (all results are p<0.05, $P_{FWE\text{-}corr}$).

GMD	Region	K	T	MNI
PANSS positive scores	R Parietal lobe precuneus	125	-3.04	6, -72, 52
	L Cerebellum posterior lobe Uvula	219	-3.45	-9, -88, -21
PANSS negative scores	L Cerebellum anterior lobe	106	-3.87	-5, -52, -23
WMD	**Region**	**K**	**T**	**MNI**
PANSS positive scores	R Inferior occipital	124	-4.03	44, -82, -8
	R Cuneus occipital	145	-3.88	21, -94, -2
PANSS negative scores	L superior frontal	311	-4.97	-8, 18, 60

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

Table 5. Clinical assessments in schizophrenia patients

	SZ-M Mean (SD)	SZ-F Mean (SD)	P value df=38
PANSS positive	17.95 (5.33)	19.65 (8.03)	0.435
Delusions	3.39 (1.09)	3.31 (1.35)	0.857
Conceptual disorganization	3.06 (0.87)	3.31 (1.30)	0.500
Hallucinations	2.06 (1.23)	3.31 (1.49)	0.941
Excitation/Hyperactivity	2.06 (0.87)	2.25 (1.13)	0.575
Grandiosity	2.11 (1.23)	2.50 (1.59)	0.429
Suspiciousness/persecution	2.28 (1.23)	3.25 (1.73)	0.066
Hostility	1.56 (0.86)	2.21 (1.15)	0.108
PANSS negative	19.50 (5.36)	21.25 (8.30)	0.434
Blunted affect	3.11 (1.02)	3.29 (1.26)	0.868
Emotional withdrawal	3.00 (1.28)	3.38 (0.31)	0.397
Poor rapport	2.72 (1.02)	3.19 (1.52)	0.296
Passive/apathetic	2.61 (1.09)	2.88 (1.15)	0.497
Difficulty in abstract thinking	2.50 (0.99)	3.19 (1.42)	0.108
Lack of spontaneity and flow of conversation	2.50 (1.15)	3.12 (1.59)	0.194
Stereotyped thinking	2.61 (0.92)	3.06 (1.29)	0.244
PANSS general	38.75 (5.27)	43.10 (12.92)	0.171
Somatic concern	2.44 (1.20)	2.62 (0.96)	0.634
Anxiety	2.61 (0.92)	3.31 (1.30)	0.076
Guilt feelings	1.67 (0.69)	2.38 (0.96)	0.018*
Tension	2.44 (0.78)	2.93 (1.29)	0.182
Mannerisms and posturing	2.67 (0.84)	2.93 (1.57)	0.528
Depression	2.23 (0.67)	2.69 (0.87)	0.132
Motor retardation	2.22 (1.11)	2.56 (1.21)	0.400
Uncooperativeness	1.56 (0.86)	2.19 (1.47)	0.130
Unusual thought content	3.11 (1.13)	3.00 (1.32)	0.793
Disorientation	1.93 (0.79)	2.31 (1.45)	0.232
Poor attention	2.89 (0.83)	3.19 (1.64)	0.501
Lack of judgment and insight	2.83 (0.79)	2.93 (1.73)	0.819
Disturbance of volition	2.44 (1.10)	2.88 (1.15)	0.272
Poor impulse control	2.44 (0.92)	2.75 (1.34)	0.440
Preoccupation	2.17 (0.86)	2.62 (0.96)	0.151
Active social avoidance	2.94 (1.21)	3.19 (1.47)	0.601

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

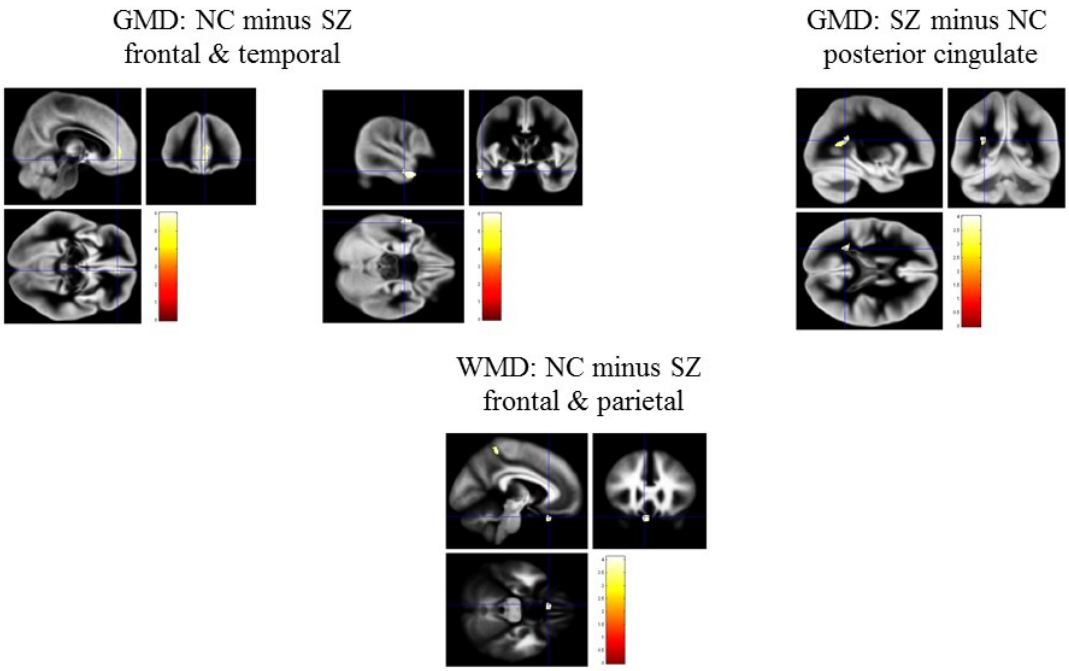
Table 6. Cognitive behavioral assessments in schizophrenia patients and normal controls

	NC		SZ		P value df=77
	Mean	**SD**	**Mean**	**SD**	
Block design from WAIS-III	12.03	3.289	9.12	3.198	0.001
Similitudes from WAIS-III	11.36	2.653	7.27	2.293	0.001
Vocabulary from WAIS-III	10.44	2.259	6.24	2.465	0.001
Raven percentile	80.56	18.320	50.99	24.827	0.001
Years of education	18.41	3.88	11.72	2.87	0.001

Cortica
www.revue-cortica.net | ISSN : 2813-1940

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

Figure 1. T-Statistic maps of the group effects between schizophrenia patients and normal controls. Hot and yellowish colors indicate density increases and decreased in each group.

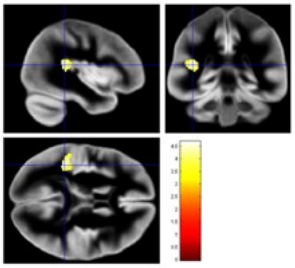


Cortica
www.revue-cortica.net | ISSN : 2813-1940
Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

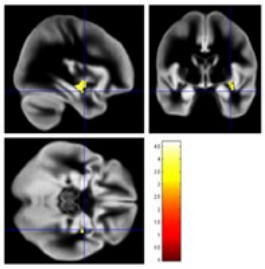
Figure 2. Positive correlations between GMD and WMD regression analysis based on symptoms

PANSS positive

GMD L Insula

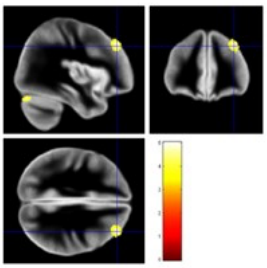


GMD R caudate



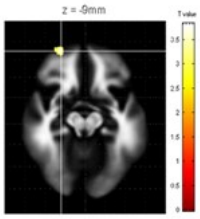
PANSS negative

GMD R middle frontal and R cerebellum



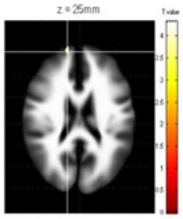
PANSS positive

WMD R middle frontal



PANSS negative

WMD R superior frontal

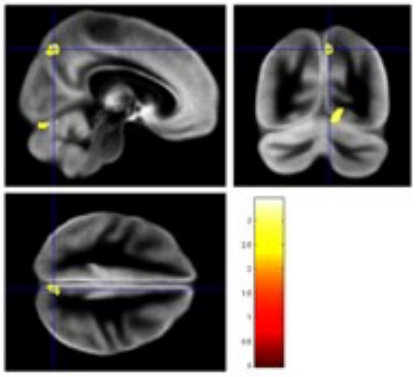


Cortica
www.revue-cortica.net | ISSN : 2813-1940
Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

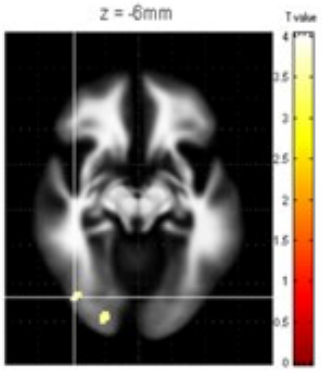
Figure 3. Negative correlations between GMD and WMD regression analysis based on symptoms

PANSS positive

GMD R precuneus and L cerebellum

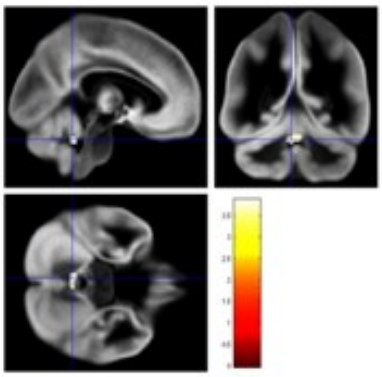


WMD R occipital and inferior cuneus

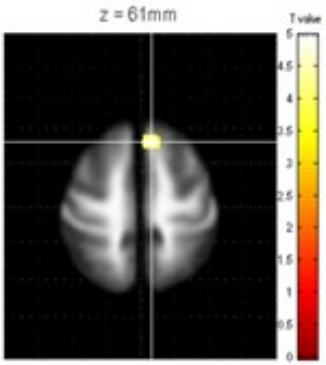


PANSS negative

GMD L Cerebellum anterior lobe

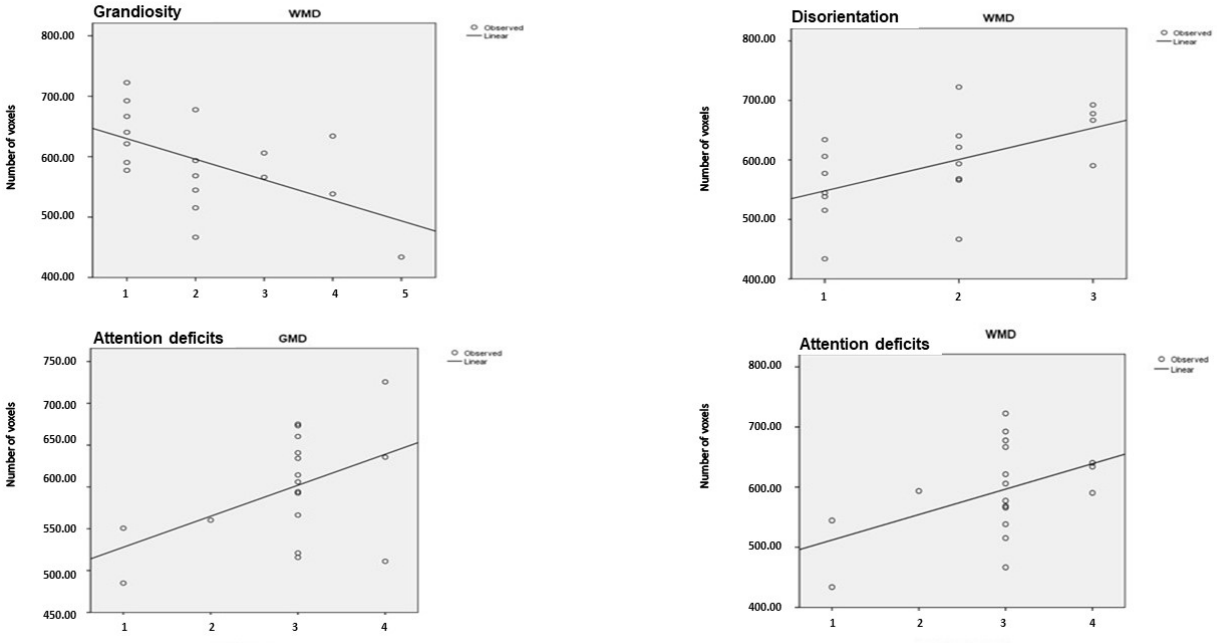


WMD L superior frontal



Cortica
www.revue-cortica.net | ISSN : 2813-1940
Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

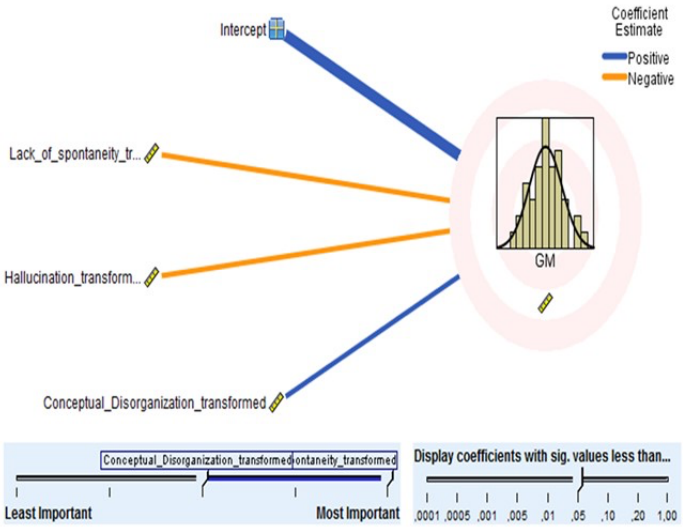
Figure 4. Regression analyses in males with schizophrenia and symptoms



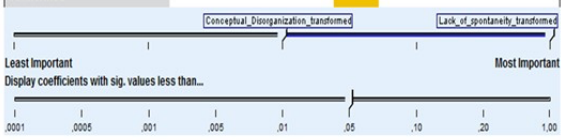
Cortica
www.revue-cortica.net | ISSN : 2813-1940

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

Figure 5. Model prediction by importance: ALM results
Coefficients
Target: Grey Matter Densities

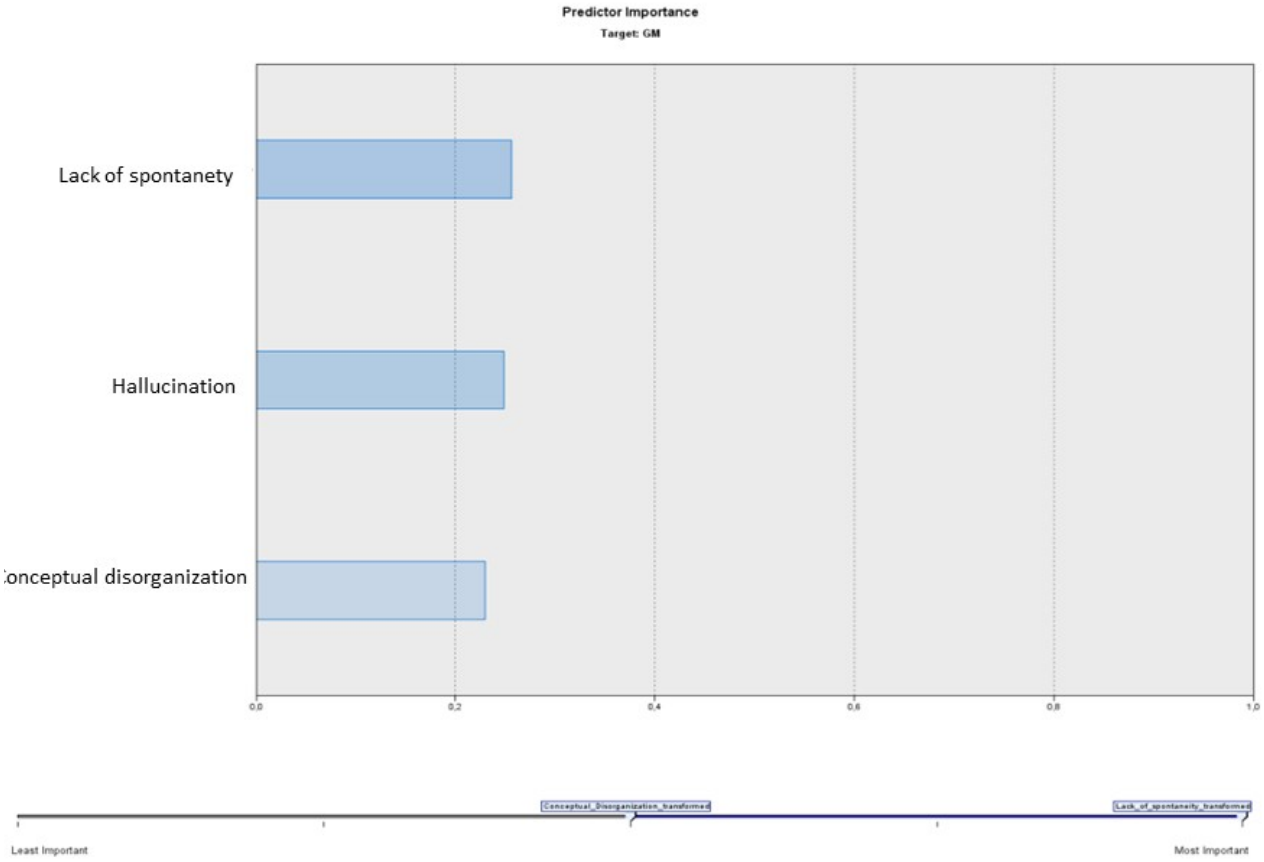


Model Term	Coefficient ▼	Std.Error	t	Sig.	95% Confidence Interval		Importance
					Lower	Upper	
Intercept	566,232	36,879	15,354	,000	491,285	641,178	
Lack_of_spontaneity_transformed	-31,801	12,919	-2,462	,019	-58,056	-5,546	0,256
Hallucination_transformed	-27,828	11,477	-2,425	,021	-51,152	-4,504	0,248
Conceptual_Disorganization_transformed	38,986	16,732	2,330	,026	4,982	72,990	0,229



Cortica
www.revue-cortica.net | ISSN : 2813-1940
Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

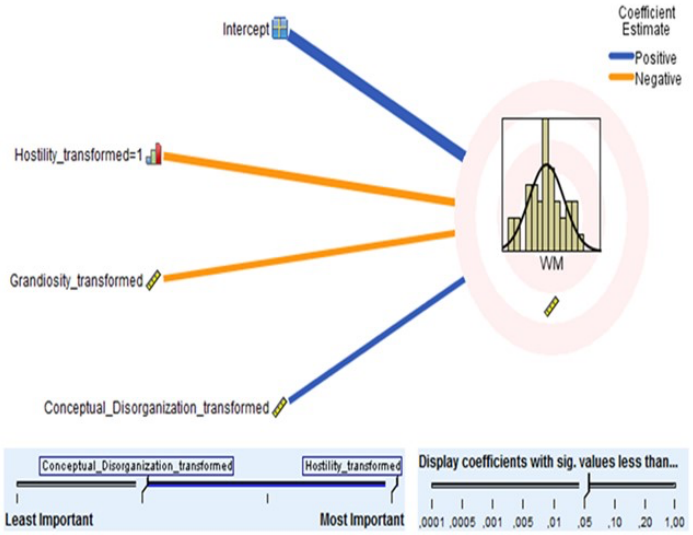
Figure 6. Model prediction by importance: ALM grey matter results



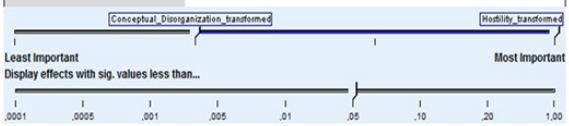
Cortica
www.revue-cortica.net | ISSN : 2813-1940

Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

Figure 7. Model prediction by importance: ALM results
Coefficients
Target: White Matter Densities



Source	Sum of Squares	df	Mean Square	F	Sig.	Importance
Corrected Model ▼	80 956,076	5	16 191,215	4,616	,003	
Hostility_transformed	40 656,283	2	20 328,141	5,796	,007	0,390
Grandiosity_transformed	27 411,593	1	27 411,593	7,815	,008	0,263
Conceptual_Disorganization_transformed	26 414,526	1	26 414,526	7,531	,010	0,253
Residual	119 249,867	34	3 507,349			
Corrected Total	200 205,943	39				



Cortica
www.revue-cortica.net | ISSN : 2813-1940
Article
Cortica 2022. *1*(2), 276-281
https://doi.org/10.26034/cortica.2022.3135

Figure 8. Model prediction by importance: ALM white matter results