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Differences in brain structure between males and females diagnosed with schizophrenia

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Résumé

Les progrès dans le domaine de la neuroimagerie cérébrale ont permis une certaine compréhension des maladies mentales comme la schizophrénie. Cependant, peu de résultats sont cohérents et ils sont souvent contradictoires, ce qui rend difficile de tirer des conclusions concrètes par rapport à la maladie.

Plusieurs facteurs jouent un rôle dans les résultats divergents et convergents : Les différentes techniques d'imagerie et les analyses, le nombre de patients inclus dans les études, l'âge des patients, l'âge de l''apparition de la maladie, les critères de diagnostic, les effets du traitement antipsychotique, le statut social, ainsi que les comorbidités, font partie de ces facteurs. Bien que les différences cérébrales entre femmes et hommes « normaux » sont bien établies, ce n'est que ces dernières années que des études en neuroimagerie de la schizophrénie ont abordé les différences homme-femme comme une explication potentielle des résultats discordants de l'imagerie cérébrale.

L'objectif de cette thèse est de comprendre le rôle du sexe (genre féminin et masculin) dans les anomalies anatomiques observées dans la schizophrénie; ceci, en réalisant des études qui contrôlent, autant que possible, l'effet de différentes variables confondantes et en utilisant des analyses d'IRM automatisées chez des patients et des sujets sains de même âge et du même sexe.

Une brève revue globale des résultats actuels dans le domaine de la schizophrénie ainsi que des résultats liés aux différences entre les sexes dans la schizophrénie vont être présentés.

La première étude visait à étudier l'influence des différences de sexe sur des mesures de la gyrification corticale de la schizophrénie. Étant donné que la schizophrénie est une maladie dont les «symptômes cliniques » ont un impact négatif sur la qualité de vie des patients qui en souffrent, nous avons exploré la relation entre la gyrification corticale et les différents symptômes de la schizophrénie chez les hommes et les femmes atteints de ce trouble psychiatrique. Le rôle du sexe sur la gyrification corticale et son association aux symptômes a été à peine étudié chez les patients atteints de schizophrénie ; c'est pour cette raison que, nous croyons que cette étude est d'une importante valeur.

Dans cette première étude, des images 3T T1 ont été acquises auprès de 48 patients atteints de schizophrénie (24 hommes [SZ-M] et 24 femmes [SZ-F]) et 48 volontaires sains (24 hommes [NC-M] et 24 femmes [NC-F]), appariés en fonction de l'âge et du sexe. Des mesures d'indice de

gyrification (IG) pour chaque hémisphère et les quatre lobes cérébraux (frontaux, temporal, pariétal, et occipital) ont été effectuées en utilisant le pipeline de CIVET, lequel est entièrement automatisé. Plusieurs résultats intéressants ont émergé: les patients avaient des valeurs inférieures importantes de l'IG global par rapport aux témoins; SZ-M avaient des valeurs d'IG hémisphériques significativement inférieurs par rapport à NC-M, cela n'a pas été observé dans les groupes de femmes. Aucune différence entre les sexes dans les valeurs de diminution de l'IG avec l'âge n'a été observés chez les témoins sains par contre, une diminution de la valeur de l'IG avec l'âge chez les patients était plus importante chez les patients homme que les patients femmes. Une détérioration plus progressive dans l'hémisphère droit dans les deux groupes de patients a été observée, tout comme des réductions significatives des valeurs d'IG en relation avec la durée de la maladie chez SZ-M, mais pas chez SZ-F.

Dans les groupes de patients, on observe des diminutions des valeurs d'IG dans les lobes frontaux bilatéraux et, le lobe occipital droit; le groupe SZ-M a montré une valeur d'IG significativement plus élevée par rapport à NC-M dans le lobe temporal droit; SZ-F a montré des valeurs d'IG significativement plus faibles dans les lobes bilatéraux frontaux, temporaux, pariétaux et le lobe occipital droit, par rapport à NC-F. Aucune corrélation significative n'a été trouvée entre les valeurs de l'IG et le profil de la symptomatologique dans les deux groupes de patients.
Etant donné que l'IG reflète, en partie, des altérations dans le développement et la connectivité cérébrale, la diminution de l'IG observée chez les patients est en accord avec le modèle de développement neurobiologique de disconnectivité dans la schizophrénie. De plus, nous soulignons l'importance de l'âge ainsi que la durée de la maladie lorsque nous comparons les hommes et les femmes atteints de schizophrénie. Cependant, nous n'avons pas observé de corrélation significative n'a été trouvée entre les valeurs de l'IG et les symptômes, ce qui est d'un intérêt particulier et inattendu compte tenu des résultats de la neuroimagerie montrant par exemple certaines corrélations entre les symptômes positifs et certaines anomalies du lobe temporal dans la schizophrénie.

Considérant ces résultats, nous avons décidé d'investiguer, dans notre deuxième étude, l'association entre les symptômes et les densités de matière grise (DMG) et de matière blanche (DMB) à la place des mesures de gyrification corticale. Nous avons utilisé la morphométrie basée sur le voxel "Voxel Based Morphometry (VBM8.0 with Diffeomorphic Anatomical Registration (Through Exponentiated Lie Algebra [DARTEL])" et la modélisation linéaire automatique

(SPSS21.0 ALM) sur les images 3T T1 MPRAGE acquises auprès de 40 patients atteints de schizophrénie (SZ) et 41 témoins sains (NC).

Nous avons trouvé que les patients atteints de schizophrénie avaient une DMG réduite dans le cortex cingulaire antérieur, le cortex temporal médian gauche et une DMG plus élevée dans le cortex cingulaire postérieur gauche par rapport aux sujets sains. Une diminution significative de DMB dans la région fronto-rectal inférieure gauche et la région pariétale postérieure gauche a été observée chez les patients comparés aux sujets sains.

Nous avons trouvé des corrélations positives entre les symptômes positifs et la DMG dans l'insula gauche et le noyau caudé droit; et entre les symptômes négatifs et la DMG dans le cortex frontal médian droite et le lobe postérieur de cervelet droit. Nous avons aussi trouvé des corrélations négatives de DMG dans la région pariétale droite (précuneus), le lobe postérieur du cervelet gauche et les symptômes positifs; ainsi qu'entre la DMG du lobe antérieur du cervelet gauche et les symptômes négatifs. En outre, des corrélations positives ont été trouvées entre la DMB dans le cortex frontal médian droit et les symptômes positifs et entre le DMB dans la région frontale supérieure droite et les symptômes négatifs. Des corrélations négatives ont été trouvées entre les symptômes positifs et la DMB dans la région occipitale inférieure droite et le cunéus occipital droit, tandis que des corrélations négatives ont été trouvées entre la DMB et la région frontale supérieure gauche.

Il est intéressant de noter que lorsque les symptômes ont été analysés par regroupement, nous avons trouvé que le symptôme de la désorganisation conceptuelle corrélait positivement avec la DMG totale et la DMB totale. L'augmentation de DMG a été associée à une diminution de la gravité des hallucinations et du manque de spontanéité; tandis que l'augmentation de DMB totale a été associée à la diminution de la sévérité de l'hostilité et des idées de grandeur. Une comparaison entre les groupes d'hommes a montré une diminution de la DMG chez les patients schizophrènes, tandis qu'aucune différences n'a été observée dans les groupes de femmes. Nous n'avons trouvé aucune corrélation entre la DMG, la DMB, le liquide cérébro-spinal, le volume total du cerveau, les symptômes individuels et la schizophrénie chez les sujets féminins. Chez les hommes atteints de schizophrénie, on observe des corrélations négatives importantes entre les idées de grandeur et la DMB; des corrélations positives entre la désorientation et la DMB. De plus on observe des corrélations entre et les déficits d'attention et de DMG et DMB. Nos résultats montrent que ces associations sont différentes chez les hommes et les femmes atteints de la schizophrénie.

La symptomatologie de schizophrénie est un mélange de déficits cognitifs et socio-affectifs. Dans ce contexte, le but de notre troisième étude est d'étudier chez les patients atteints de la schizophrénie des DMG et DMB et leur relation avec l'acuité mnésique avec des contenus émotionnelles (négatives, positives et neutres) ainsi que étudier l'effet des différences de sexe sur nos résultats.
Quarante et un patients droitiers, traités par antipsychotique, souffrant de schizophrénie (SZ) et 40 témoins sains (NC), tous droitiers, ont participé à l'étude. Nous avons utilisé des images de l'*International Affective Picture System (IAPS*), une banque d'images émotionnelles, et de l'IRM.
On observe chez les témoins sains des corrélations entre les valeurs élevées de DMG du cortex pariétal postérieur, du lentiform, du putamen, noyau caudé, le cortex orbitofrontal inférieur gauche et la reconnaissance des images négatives. On observe des corrélations entre la DMG dans la région temporale gauche, fusiforme et la reconnaissance des images positives ; et également dans le cervelet antérieur gauche et l'acuité des images neutres. Chez les patients on observe des valeurs élevées des DMG dans le cortex occipital inférieur gauche et la reconnaissance des images négatives, mais aucune corrélation entre la capacité de reconnaissance des images positives ou neutres.
Nous avons observé chez les témoins sains: des relations significatives entre la DMB dans le cortex pariétal postcentral gauche et la capacité de reconnaître des images négatives; dans le cortex temporal inferieur gauche, le cortex pariétal gauche (précuneus), le cortex frontal gauche et la capacité de reconnaissance des images positives; des valeurs de DMB du cortex temporel médian et l'acuité des images neutres.
Les patients atteints de schizophrénie ont montré des relations significatives entre de DMB dans le cortex occipito-lingual gauche et la reconnaissance des images négatives ; dans le cortex pariétal angulaire gauche et la reconnaissance des images positives ; et dans le cortex temporal supérieur droit et les images neutres. Les différences de sexe dans la schizophrénie ont été observées : chez les patients de sexe masculin, des corrélations négatives ont été trouvées entre les DMB et la capacité de reconnaître des images négatives et positives. Chez les hommes sains, nous avons trouvé des corrélations positives entre des valeurs totales de DMG et la capacité de reconnaître des images négatives. Nous n'avons pas observé de corrélations dans les groupes de femmes. Ces résultats soutiennent l'hypothèse de l'atrophie fronto-temporale régionale chez les patients schizophrènes. Toutefois, nous notons qu'ils ont des augmentations relatives des valeurs de DMB dans le cortex occipito-pariétal.

Nous avançons l'hypothèse que les déficits mnésiques chez les patients sont liés à des perturbations dans la coordination des réseaux cérébraux, ce qui peut être affecté par des déficits structuraux plus évidents chez les patients masculins. Par conséquent, nous préconisons que les futures études devraient utiliser le connectome ou l'approche « réseaux cérébraux » pour étudier l'impact du sexe (genre masculin-féminin) sur les déficits cognitifs et symptomatologiques dans la schizophrénie.
Nos résultats globaux soulignent l'importance de la différence entre homme et femme dans la modulation de manifestations cliniques et fonctionnelles de la schizophrénie. Ainsi, nous croyons que le contrôle des covariables comme l'âge, la durée de la maladie et le statut social est insuffisant et que les études futures sur la schizophrénie devraient systématiquement séparer les hommes des femmes, afin de mieux comprendre cette maladie mentale complexe et dévastatrice.

Mots-clés: Schizophrénie, les différences de sexe, l'imagerie par résonance magnétique, les symptômes, les déficits cognitivo-affectifs, indice de gyrification, substance grise, la substance blanche.

Abstract

Advances in cerebral neuroimaging techniques have helped our understanding of mental illnesses, such as schizophrenia. Few findings remain consistent and are often contradictory, making it difficult to draw informative conclusions about the disease. Several factors play a role in both diverging and converging results. Imaging technique and analyses, number of patients involved, age of patients, age at onset of the disease, diagnostic criteria, antipsychotic treatment effects, social status, comorbidities, are among some of the reasons. Despite well established cerebral sex differences in healthy population, it is only in recent years that neuroimaging studies in schizophrenia have addressed sex differences as a major possible explanation for discrepant neuroimaging finding.

The aim of this thesis is to help understand the role of sex on brain structures in schizophrenia, by conducting studies that control as much as possible for other variables and by using MRI automated analyses for patients and controls matched for age and sex. This work will briefly present findings in schizophrenia in general, and then an extensive review of the literature on sex differences in schizophrenia will be presented. From it, we are able to conclude that sex differences have been reported with rare exception in almost all aspects involved in the life of patients with schizophrenia.

Chapters

1. The first study investigated sex differences in cortical gyrification in schizophrenia patients (SZ). In addition, considering that schizophrenia is a disease of "clinical symptoms" that determine the quality of life of patients afflicted by it, we explored the relation between cortical gyrification and symptoms in males and females with schizophrenia. The role of sex on cortical gyrification and its association with symptoms has been scarcely investigated in patients with schizophrenia. In this study, 3T T1 images were acquired from 48 schizophrenia patients (24 males [SZ-M] and 24 females [SZ-F]) and 48 normal controls [NC] (24 males [NC-M] and 24 females [NC-F]) matched for age, sex, and handedness. Gyrification Index (GI) analyses for each hemisphere and four cerebral regions (frontal, temporal, parietal, and occipital) were performed using the fully automated CIVET pipeline. Patients had significant lower values of the overall GI relative to normal controls and SZ-M had significant lower right hemispheric GI values compared to NC-M. This was not observed in either NC-F or in SZ. No gender difference in GI values decreases with

age were observed in NC. In patients, GI decreases with age were greater in SZ-M than SZ-F, with a more progressive deterioration in the right hemisphere in both patient groups. Significant GI value reductions in association with duration of illness were observed in SZ-M but not in SZ-F. Patient groups had lower GI in bilateral frontal, temporal, and parietal lobes than controls. SZ-F had significant lower GI values in left frontal, bilateral temporal and left parietal lobe compared to NC-F. No significant correlations were found between GI values and symptom scores in either group of patients. Since GI reflects, in part, alterations in cerebral development and connectivity, the decrease in GI observed in patients is in agreement with the neurodevelopmental model of disconnectivity in schizophrenia, and may explain the worse prognosis and social outcome observed in male patients. Furthermore, we emphasize the importance of age and duration of illness when comparing males and females with schizophrenia. Observed differences between male and female patients may reflect a more diffuse and generalized cortical loss in males. Female patients had cortical loss in specific regions, while preserving cortical gyrification in compensatory regions. Our latter finding -no significant correlation between GI values and symptom scores- was of particular interest and was unexpected in view of neuroimaging findings of correlations between positive symptoms and temporal lobe abnormalities.

2. In the second study, we examined the association between symptoms and brain structure using gray (GMD) and white matter (WMD) densities. Voxel-based morphometry (VBM8.0 with Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra [DARTEL]) and Automatic Linear Modeling (SPSS21.0 ALM) were used on 3T T1 MPRAGE images acquired from 40 schizophrenia patients (SZ) and 41 normal controls (NC). We found that SZ had lower GMD in the anterior cingulate cortex and left middle temporal gyrus, and higher GMD in the left posterior cingulate in comparison to NC. SZ had significantly lower WMD in the left inferior fronto-rectal and the left posterior parietal regions in comparison to NC. Significant positive correlations were found between positive symptoms and GMD in the left insula and right caudate, and between negative symptoms and GMD in the right middle frontal and the posterior lobe of the right cerebellum (uvula). Inverse relationships between GMD in the right parietal (precuneus), the left posterior lobe of the cerebellum (uvula) and positive symptoms, and between GMD in the left anterior lobe of the cerebellum and negative symptoms were observed in SZ. In addition, positive correlations were found between WMD in the right middle frontal lobe, and between positive symptoms and WMD in the right superior frontal region with negative symptoms. Negative

correlations were found between positive symptoms and WMD in the right inferior occipital and the right occipital cuneus, while negative symptoms correlated negatively with the WMD of the left superior frontal.

When symptom clusters were analyzed, conceptual disorganization symptom positively correlated with both total GMD and WMD. While increases in GMD were associated with decreased severity of lack of spontaneity and hallucinations symptom, increases in total WMD were associated with decreased severity of hostility and grandiosity symptoms. Comparison between male subjects revealed decreased GMD in male schizophrenia patients, while no differences were observed between females across groups. No correlations were found in female groups between GMD, WMD, CSF, or total brain volume and individual symptoms. In males with schizophrenia, significant negative correlation between ideas of grandiosity and WMD, a positive correlation between disorientation and WMD, and attention deficits and GMD and WMD were found. The current data suggest region-specific GMD and WMD association with negative and positive symptoms. In addition, it reveals that such associations are different in male and female schizophrenia patients.

3. The third study investigated the relationships of GMD and WMD with memory accuracy for emotionally negative, positive, and neutral pictures in schizophrenia patients relative to normal controls. Schizophrenia is characterized by an amalgam of cognitivo-socio-emotional deficits. The relationship between emotion processing on cognition and neurobiological underpinnings merit more attention than it has received so far. Memory deficits are among the most common deficits in schizophrenia and have a widespread impact on cognition in general. Additionally, consistently with the major theme of the present thesis, we investigated the effect of gender on the observed effect. Forty one, right-handed medicated patients with schizophrenia (SZ) and 40 right-handed normal controls (NC) matched by age and sex were assessed for memory accuracy using negative, positive and neutral pictures taken from the International Affective Picture System (IAPS). Imaging methods and analyses were similar to our second study. Fifteen minutes after presentation of selected IAPS images (incidental encoding), subjects were asked to recognize the previously seen images among other images. We found higher GMD in NC in the right posterior parietal cortex, lentiform, putamen, and caudate, as well as the left inferior orbitofrontal cortex, in relation with the negative images accuracy. NC had higher GMD in the left temporal and fusiform regions in relation with the positive images accuracy, and higher GMD in the left anterior cerebellum in

relation with neutral images. Schizophrenia subjects had higher GMD in the left inferior occipital cortex in relation with the negative images accuracy, but GMD was not correlated with positive or neutral images accuracy in this group. WMDs correlations were higher in NC in the left postcentral parietal region for negative images; in the left inferior temporal, left precuneus parietal, and left frontal regions for positive images; and in the left middle temporal region for neutral images. Schizophrenia patients had higher WMD in the left lingual occipital for negative images; in the left angular parietal for positive images; and in the right superior temporal region for neutral images. While examining the two sexes separately, we observed inverse correlations between WMD and both negative and positive pictures in male patients. In addition, only in male controls, GMD positively correlated with negative pictures and this correlation was absent in female SZ subjects and NC females. These findings support the hypothesis of fronto-temporal regional atrophy in schizophrenia. Schizophrenia patients have relatively increased occipito-parietal WMD, advancing the hypothesis that the core pathophysiological problem underlying recall memory in SZ may be related to disruptive alterations in the coordination of large-scale brain networks, and this may be affected by structural deficits that are more evident in male patients. It is recommended that future studies should use the connectomes or the brain networks approach to investigate the effect of sex on memory deficits in schizophrenia.

Our overall findings point out to the importance of sex in modulating the clinical and functional manifestations of schizophrenia. We believe that controlling for covariates as age, duration of illness, social status, etc. is insufficient and that future studies in schizophrenia should systematically separate male and female findings, if we wish to understand this complex and devastating mental illness.

Keywords: Schizophrenia, sex differences, magnetic resonance imaging, positive and negative symptoms, cognitivo-emotion deficits, gyrification index, voxel based morphometry, gray matter densities, white matter densities.

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Abbreviations

2D	2 dimensional
3D	3 dimensional
3T	3 Tesla
AICC	Akaike's Information Criterion Corrected
ALM	Automatic Linear Modeling
ANCOVA	Analysis of covariance
ANOVA	Analysis-of-variance
BA32	Broadman Area 32
BDNF	Brain-derived neurotrophic factor
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CCTCC	Cortico-cerebellar-thalamic-cortical circuit
CIHR	Canadian Institutes of Health Research
CIVET	Brain image-processing pipeline for fully-automated corticometric, morphometric and volumetric analyses of magnetic resonance
CLASP	Constrained Laplacian Anatomic Segmentation using Proximity
CSF	Cerebral spinal fluid
CT scans	Computerized tomography
DARTEL	Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra
DMB	Densité de la matière blanche
DMG	Densité de la matière grise
DRSC	Developmentally reduced synaptic connectivity
DSM-IV	The Diagnostic and Statistical Manual of Mental Disorders, fourth edition
DSM-V	The Diagnostic and Statistical Manual of Mental Disorders, fifth edition
ERP	Event Related brain Potentials
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
FOV	Field of view
FRSQ	Fond de recherche en santé du Québec
GABA	Gamma-aminobutyric acid
GI	Gyrification index

GLM	General Linear Model
GM	Gray matter
GMD	Gray matter density
GMV	Gray matter volume
IAPS	International Affective Picture System
ICD-10	International Statistical Classification of Diseases, 10^{th} revision
IG	Indice de gyrification
IGH	The Institute of Gender and Health
IRM	L'imagerie par résonance magnétique
IQ	Intelligence quotient
L	Left
MATLAB	Matrix Laboratory
MNI	Montreal Neurological Institute
MPRAGE	Magnetization Prepared Rapid Gradient Echo Imaging
MRI	Magnetic resonance imaging
MSUC	Meiotic suppression of unpaired chromosomes
NC	Normal controls
NC-M	Normal control males
NC-F	Normal control females
NFG	Nerve growth factor
NICE	The National Institute for Health and Care Excellence
NMA	Negative memory accuracy
NOC	National Occupational Classification NOC
OAR	Orbitofrontal cortex and amygdala ratio
OC	Obstetrical complications
PANSS	Positive and negative syndrome scale
$P_{FWE-corr}$	Familywise error rate
PMA	Positive memory accuracy
PORT	Patient Outcomes Research Team
QT	QT; the time between the start of the Q wave and the end of the T wave in the cardio electric cycle

R	Right
SANS	Scale for the Assessment of Negative Symptoms
SZ	Schizophrenia patients
SCID	Clinical Interview for DSM-IV
SD	Standard deviation
SNR	Signal to noise ratio
SPM8	Statistical Parametric Mapping version 8
SPM-t	Statistical parametric map of the t-statistic
SPSS 17	Statistical Package for the Social Sciences, version 17.0
SPSS 21	Statistical Package for the Social Sciences, version 21.0
SZ-M	Males with schizophrenia
SZ-F	Females with schizophrenia
TE	Echo Time
TR	Repetition Time
VBM	Voxel based morphometry
VBR	Ventricular-brain ratios
WHO	World Health Organization
WM	White matter
WMD	White matter density
ZMA	Neutral memory accuracy

Thank you

I dedicate this work to my parents, my wife, and my children.

Working as a clinician and at the same time on my Ph.D., has been a great challenge. There were moments when I thought it was impossible, however I feel blessed to be surrounded by people who inspire me, encourage me, and most of all believe in me. Here I would like to take the time to thank them for the force they have ignited in me, especially at the times when the road was rough and the purpose of what I wanted to achieve was distorted. I have to start where all things start…with my parents, you taught me the importance of perseverance and that it is "never too late", you taught me the magical effect of *"...it's ok...you're almost there!"*. You inspired me by being yourselves a model to follow and by obtaining your degrees decades before. I want to thank you for that, for your unconditional love and for doing all what you could to provide me with the bases that would make me the independent and the "not afraid of challenges" person I am now.

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1 Introduction

1.1 History of schizophrenia

The term schizophrenia, which literally means "split mind or mind torn apart" was first used by Euegen Bleuler (1911). Bleuler defined schizophrenia as essentially a splitting of thoughts (cognition) from feelings (emotion). Bleuler considered symptoms such as loose associations, blunted affect, ambivalence, and autism as the core psychopathologies of the illness. Bleuler defined a set of basic symptoms considered to be unique to the disorder and present in all patients with the disorder. The pathogenesis and prognosis were considered to be variable where patients may present a stable, deteriorating, or improving clinical tableau after the first onset (1). Kraepelin (1919) used the term dementia praecox to describe schizophrenia; he believed it was a disease with a single etiology and a distinct pathogenesis (2). More specifically, Kraepelin described the disease as neurodegenerative with a dementia-like characteristics that started in adolescence or early adulthood. Symptoms described were catatonia, hebephrenia, and paranoid dementia. Positive symptomatology in schizophrenia was conceptualized by Schneider (1959) who described primary symptoms of schizophrenia like hallucinations as disease specific (3). Since then several authors have reported these symptoms in other somatic/physical (4, 5), neurological (6), genetic (7-9) and psychiatric pathologies (10).

1.2 Overview

Schizophrenia is a severe, chronic and complex psychiatric disorder characterized by a significant functional decline impacting cognitive, affective and social domains (11). Its complexity is reflected in the heterogeneous clinical presentation with symptoms ranging from hallucinations and delusions, disorganized speech and behavior, to flat affect, lack of motivation, and cognitive deficits linked to areas of attention, memory and executive functions (12, 13). In addition, schizophrenia heterogeneity is further complicated by the presence of important sex differences with respect to age at disease onset, symptomatology, medication responsiveness, prognosis, social outcomes, comorbidities, premorbid functioning, and structural brain

abnormalities (14-21). Schizophrenia typically manifests during late adolescence or early adulthood between the ages of 16 and 30 years. It usually has a progressive and insidious onset over several years. Approximately 10-15% of schizophrenia patients commit suicide (22, 23) and almost half of the patients will have attempted suicide during their lifetime (24-26). Mortality in schizophrenia population for all causes, has been shown to be two to threefold higher than in the normal population (27).

Schizophrenia is characterized by a large array of symptoms that can be seen in other mental diseases. Symptoms are classified under three broad types: I- Positive symptoms (i.e., conceptual disorganization, delusional ideation, altered perceptual experiences as acoustic- verbal, tactile, and gustatory hallucinations, hostility, grandiosity, and paranoid ideation). II- Negative symptoms (i.e. blunted affect, emotional withdrawal, passive/apathetic social withdrawal, anhedonia, avolition/apathy, and poverty of speech). III- Cognitive symptoms (i.e. poor attention, lack of judgment and insight, unusual thought content, difficulties in abstract thinking, disorientation in time and space, alteration in the perception of self and one's situation, and concentration and memory deficits.

Criterion-based systems have been developed to decrease the complexity and improve the reliability of diagnosis. These systems include the International Classification of Diseases, tenth edition (ICD-10) (1994), used mostly in European countries, the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (1994), and more recently the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) (2013) which describe characteristic symptoms of schizophrenia (28). The two systems have some fundamental differences (for details please see table Y) (29). The release of the DSM-V introduced two changes to DSM-IV Criterion A for schizophrenia: (1) bizarre delusions and special auditory hallucinations (Schneiderian first-rank symptoms) are not considered as schizophrenia specific and (2) that the individual must have at least one of the core "positive symptoms": delusions, hallucinations, and disorganized speech for a reliable diagnosis of schizophrenia. Both DSM-IV and V criteria require the presence of social and occupational dysfunction (30). Subtypes of schizophrenia were removed because of lack of diagnostic and course stability. Since the release of DSM-V several clinicians and researchers questioned, criticized, and debated the coherence of its criteria for schizophrenia (29, 31-34). Overall, diagnostic criteria improve reliability and improve clinical communication.

The emphasis on psychotic symptoms (delusions and hallucinations) in the diagnosis of schizophrenia has overshadowed the importance of other symptoms that are less acute, particularly those symptoms that have a great negative impact on social and interpersonal relations. Symptoms of social and cognitive deterioration are usually present before and persist after remission of the acute phase of positive symptoms. Interestingly, a recent meta-analysis demonstrated that contrary to the current belief, negative symptoms were found to decrease in almost all schizophrenia outpatient samples (35). These findings suggest that negative symptoms may improve over time to a greater extent than what has previously been assumed (36-38). Blanchard & Cohen (2006) examined the structure of negative symptoms in schizophrenia and whether they represent an independent group of symptoms. They also investigated if negative symptoms are themselves subtyped. They consistently found across studies that negative symptoms seemed to be independent from positive, affective, depression, anxiety, or disorganization symptoms. Two separate clusters of negative symptoms were consistently identified in the literature: diminished expression and anhedonia-asociality (39).

The relation between negative symptoms (e.g. apathy, avolition, blunted affect) and loss of social and interpersonal abilities are now well documented in the literature (40, 41). Patients suffering from schizophrenia are typically unable to continue their education or maintain their employment (42). Tsang et al, (2010) found that cognitive functioning, negative symptoms, social, community, and mental health support were significant predictors of employment outcome Positive symptoms, substance abuse, gender and hospitalization history were found to be non-significant predictors (43). Negative symptoms may be the best symptomatic predictor of functioning in individuals with early psychosis is an important treatment target to improve remission (44, 45)

A cornerstone theory to explain schizophrenia symptoms is the ‘dopamine hypothesis’ (46) It was posited that positive symptoms were related to dopamine neuron overactivity in the mesolimbic pathway, and that the negative symptoms were related to underactivity of dopamine neurons in the prefrontal cortex (47-49).

1.3 Epidemiology of schizophrenia

Schizophrenia is a severe mental disease with a combined economic and social burden (50) ranking among the world's top causes of disability in life-years (51, 52). Lifetime prevalence is between 0.7 and 1% worldwide (53-55). More recent studies suggest that the rate of 1% could be an overestimate and that arguably, the prevalence of the disorder is typically higher in developed than in developing countries, and higher in migrant groups than in native-born populations (56, 57). Additionally, a higher prevalence of schizophrenia among lower socio-economic classes within communities has been steadily reported over the past century (58-60). Incidence, which represents the annual number of newly diagnosed patients in the population varies significantly in the literature (61, 62). McGrath and colleagues (2008) have reported that the median incidence of schizophrenia was 15.2/100,000 persons and that the central 80% of estimates varied significantly between 7.7 and 43/100,000 persons. In addition, the authors found urbanity, migration, and male gender to be associated with higher developing of the disorder. The changeability in incidence rates might be attributed to changes in diagnostic approaches (27).

1.4 Etiology of schizophrenia

Factors that may play a role in the development of schizophrenia include , perinatal/prenatal viral infections (63, 64), obstetric complications, hypoxia at birth, Rh incompatibility, famine and malnutrition, severe environmental stresses, urbanity, winter births, and heritability as demonstrated by twin and adoption studies. To date the etiology of schizophrenia remains unclear. Several theories on the origin of schizophrenia have been proposed. One central hypothesis is the neurodevelopmental theory, which posits that neurodevelopmental changes in utero through young adulthood play a role (65-70). Neurodevelopmental factors are influenced by the combined impact of genetics and prenatal events triggering pathological processes during adolescence (71-73). The mechanism by which these factors lead to schizophrenia remains unknown. Neurodevelopmental anomalies during uterine development in the 1st and 2nd trimesters have been proposed to result in pathological neural circuitry during critical development in adolescence (74) especially if the adolescent is exposed to stress or abused drugs (65, 71, 75-80).

Recent advances in neuroimaging, genetics, and neuropharmacology have indicted the pivotal role played by abnormalities in key neurotransmitters (i.e. dopamine, serotonin, glutamate, GABA, acetylcholine, and noradrenaline) in development of schizophrenia (81-91).

The risk of developing schizophrenia is considerably higher in individuals with an affected family member. This risk increases with the degree of genetic proximity: it is higher in persons with first-degree relative with the disorder (92, 93). Twin and adoption studies of schizophrenia consistently show higher concordance rates in monozygotic of approximately 50 to 80% in comparison with approximately 17% in dizygotic twins(94-99). Approximately 20 to 50% of monozygotic twins are discordant for schizophrenia, suggesting a role for the environmental factors (100, 101). There is little evidence available to isolate one specific or group of genes in schizophrenia (60), although it is likely to be a polygenic/multifactorial disease (60, 102, 103). Additionally, both pre- and perinatal complications (e.g. maternal influenza, fetal hypoxia), comorbidities as obsessive-compulsive disorder and other environmental elements (e.g. season of birth, cannabis use) have been linked to a substantial increase in risk for schizophrenia (60, 104-108). Lastly, subjects with a family history of schizophrenia were found to have a lower average age at onset (109)

1.5 Cognition in schizophrenia

Schizophrenia was a term created by Bleuler in 1911 to characterize the fragmentation and disintegration of the mind and behavior of this disorder (1). Since then, research has intensively investigated the splitting of thoughts, feelings, and actions in schizophrenia (110-114). Specifically, studies have addressed how and why these functions are dissociated (115-117). Despite the robust evidence for the influence of emotion on cognition and vice versa, the nature of these interactions and their role in psychotic symptoms are not yet clearly understood (118-120).

A meta-analysis by Reichenberg (2010) revealed that schizophrenia patients manifest a wide range of cognitive deficits, including reduced capacity in executive function, declarative memory, and processing speed. Other cognitive deficits encompass working memory, motor speed, language and perception deficits (121). Chronic schizophrenia patients have disturbances in both selective attention and maintaining attention (122-124). Neuroimaging studies show that these deficits are associated with a diminished activation in superior temporal and frontal gyri, cingulate,

thalamus, and basal ganglia. Abnormal activation correlated with positive and negative symptoms (125). Increased activation in other prefrontal areas in patients is thought to be compensatory (126).

A meta-analyses by Fioravanti et al., (2012) reported that executive functions are severely affected in patients with schizophrenia (127). Functional neuroimaging studies on executive function show that schizophrenia patients activate a similar neural network when compared with healthy subjects; however, patients had altered activity with deficits in the dorsolateral prefrontal cortex, anterior cingulate and mediodorsal nucleus of the thalamus.

Memory deficits are among the most common deficits in schizophrenia with widespread impacts on other cognitive problems, ranging from attentional and visuo-spatial deficits to problems in higher cognitive functions such as reasoning, planning and problem solving (124, 128-137). Deficits in working memory have been associated with hypoactivation in the medial temporal lobe (137). A meta-analysis of episodic memory in patients with schizophrenia showed a robust pattern of decreased cerebral activations in the prefrontal cortex, cerebellum and temporal regions (138). Temporal lobe neuroanatomical abnormalities, contributing to memory deficits, observed in structural neuroimaging studies remain among the most robust findings (139-142).

Overall, memory impairments in schizophrenia are considered to be core endophenotypes because they are common, are relatively stable across the course of the illness, are present regardless of psychotic symptoms, and are found to a lesser degree in unaffected relatives (143).

1.6 Emotion in schizophrenia

Affective deficits are characteristics of schizophrenia and can be summarized in three general domains: perception, expression, and experiencing of emotions (144-154). Habel et al., (2000) assessed discrimination and experience of emotion (mood induction) in three different ethnic groups of patients with schizophrenia (American, German, and Indian) using happy, sad, and neutral facial expressions of Caucasian actors. Face discrimination performance was impaired across the three patient groups in comparison with healthy controls. This finding is consistent with the literature on schizophrenia features being stable across cultures (155, 156). A recent meta-analysis by Barkl and colleagues (2014), found that deficits in facial emotion identification were already present in patients at the onset of psychosis, and that emotion identification impairment

represents a trait susceptibility marker, rather than a consequence of the disease (144). Impairments in perception of facial emotions vary from moderate to severe in schizophrenia (146), and appear to be influenced by clinical and demographic factors (151). Collectively, these studies provide substantial support for a socio-emotional deficit in schizophrenia (147, 149, 157-162). Disturbances in socio-emotional cognition observed in patients with schizophrenia may represent an abnormal interaction between frontal lobe and its functionally connected cortical and subcortical areas (163). Significant variations in deficits are not explained by age, education, or gender. Severity of clinical symptoms and duration of illness were associated with greater deficits in emotion processing (164).

Inconsistent findings of emotional valence and arousal deficits are reported in schizophrenia patients. Patients with anhedonia show deficits in valence but not in arousal compared to controls. Reduced valence experience was associated with increased degree of anhedonia in patients and controls (165). Schizophrenia patients with flat affect seemed to rate emotional valence similarly to healthy controls however they have reduced neural activity in the anterior cingulate, right parahippocampal gyrus and multiple visual areas (166). Foucher et al, (2011) showed that coupling arousal with cognitive tasks improve cerebral activity in hypoactive regions in patients with schizophrenia (167). In healthy population, a weak but consistent V-shaped relation between arousal and valence was reported. This relation showed a large variation at the individual level depending on person or circumstances (Kuppens et al., 2013).

Many studies have identified structural and functional abnormalities in the medial prefrontal cortex, orbitofrontal and anterior cingulate gyrus regions pivotal to the regulation of affective states and emotional behavior in schizophrenia (168). Additionally, abnormalities of the amygdala have been reported during processing of emotions in patients with schizophrenia (153). Gur and colleagues (2004) (169) found that schizophrenia patients had no activation of the limbic regions during emotional valence discrimination tasks. Conversely, a study by Kosaka et al., (2002) found that schizophrenia patients activated their amygdala bilaterally during negative face discrimination tasks in comparison to healthy controls who activated the right amygdala alone (170). Interestingly, studies comparing subgroups of schizophrenia patients show varying degrees of emotional impairments (108, 171-184). Impairment in emotional functioning is closely associated with to poor clinical and social outcomes including unemployment, social dysfunction,

and worse prognosis (42, 185-188).Cognitive and affective deficits in schizophrenia have been associated with altered multisensory integration also termed perceptual incoherence (189). Postmes et al., (2014) theorize that perceptual incoherence in schizophrenia may evoke incoherent self-experiences including depersonalization, ambivalence, diminished sense of agency, and 'loosening of associations' between thoughts, feelings and actions. Thus patients with schizophrenia are unable to apprehend the world in holistic manner or to experience the unity of his/her self, thoughts and feelings (190)

1.7 Pathogenesis of schizophrenia

The combined effects of gene and environment have been associated with brain morphometric abnormalities in schizophrenia. These abnormalities are suggestive of alterations in synaptic, dendritic, and axonal organization, resulting in abnormalities in connectivity between cerebral neural circuitry (141, 191-198). Environmental and developmental processes further impact these abnormalities (22, 77, 199).

It has been postulated that schizophrenia is a result of disturbances in the later phases of cerebral cortical development especially in the last phases of neuronal migration and pruning of cortical connections (e.g. Jones, EG, 1995, 1997)(200, 201). A disturbance of migration or preprogrammed pruning in the white matter immediately below layer VI of the cortex causing a failure to establish normal patterns of connections in the overlying cortex was proposed as an explanation. This vulnerable circuitry is associated with altered gene expression for neurotransmitter and receptor-related molecules, which in turn could lead to schizophrenia (200, 201). Based on studies showing altered neuronal density, Selemon and Goldman-Rakic (1999) proposed that reduction in prefrontal cortex interneuronal neuropil compromised cell structure, and impoverished neuronal connectivity caused deficits in functional communication between neurons. They reported that the increased neuronal density seen on histological examination as reduced neuropil without neuronal loss, indicated a subtle loss of connections between neurons with devastating consequences on cortical function in patients with schizophrenia (202). Andreasen et al., (1998) proposed a connectivity model in schizophrenia that leads to what the authors termed *cognitive dysmetria.* This model implicates dysfunction of the cortico-cerebellar-thalamic-cortical circuit (CCTCC) connectivity in schizophrenia (203).

McGlashan and Hoffman (2000) proposed that schizophrenia resulted from developmentally reduced synaptic connectivity (DRSC). The model suggests that schizophrenia arises from critically reduced synaptic connectedness because of developmental disturbances of synaptogenesis during gestation and early childhood and/or synaptic pruning during adolescence. The DRSC model describes reduced synaptic density in prefrontal and other areas of association cortex as the "final common pathway" to the symptoms and course of schizophrenia (198). Buckley et al., (2007) found that disturbances in brain-derived neurotrophic factor (BDNF) and nerve growth factor (NFG) might contribute to the pathogenesis of schizophrenia. These disturbances were found in first-episode patients. The preceding findings point to the presence of altered connectivity patterns in schizophrenia. These alterations may manifest as micro (i.e. the synaptic/neural level) or macro (i.e. white matter wiring/cabling level) circuit anomalies (204).

1.8 Treatment of schizophrenia

Schizophrenia remains an incurable mental illness partly due to the heterogeneity of symptoms and the limited efficacy of current treatments (205-209). Existing treatments aim at managing the symptoms in their acute phase and attaining a clinical stability over time using multidisciplinary approaches such as medication, cognitive remediation, individual and group psychotherapy, social enforcement and integration, appropriate housing, adapted employment and financial aid, and supportive family education (210). These approaches are recommended guidelines in North America by The Schizophrenia Patient Outcomes Research Team (PORT) (2009) and The National Institute for Health and Care Excellence (NICE) in UK (2009).

In general, typical antipsychotics, also termed first generation antipsychotic drugs have been shown to be effective in improving positive symptoms and in decreasing relapses of schizophrenia, while having little therapeutic effects on negative symptoms, mood symptoms and cognitive deficits (11, 211-215). Atypical antipsychotics are characterized by fewer extrapyramidal side-effects (i.e. pseudo Parkinson's-like symptoms), better efficacy in treatment of negative symptoms, fewer prolactin disturbances, and additional benefits on cognitive deficits (216). It should be noted however, that recent data regarding efficacy of atypical versus typical antipsychotics does not support the greater benefit of atypicals for management of negative symptoms or for cognitive amelioration (217-222). Clozapine, an atypical antipsychotic, has also

shown more efficacy in some non-respondent patients (223-227). A multicenter randomized double blind controlled study demonstrated that olanzapine had the lowest rates of discontinuation and was most strongly associated with metabolic syndrome and weight gain. The efficacy of the first generation antipsychotic perphenazine appears similar to that of the second generation antipsychotics quetiapine, risperidone, and ziprasidone (219, 228-231). Observational and naturalistic studies report that: patients treated with olanzapine and clozapine had somewhat better outcomes than patients treated with other atypical or typical antipsychotics in terms of response, relapse, remission and treatment discontinuation. Additionally, atypical antipsychotics had also a lower frequency of extrapyramidal symptoms and anticholinergic use compared to typical antipsychotics (e.g. haloperidol, flupenthixol, fluphenazine, perazin and zuclopenthixol). Weight gain was associated with all antipsychotics, however it was greater with olanzapine and clozapine (229).

Other treatment interventions are gaining momentum in the management of schizophrenia, including cognitive training, psychoeducation, social skills training, cognitive behavior therapy and cognitive remediation therapy (232-248) The lack of consensus on assessment methods of efficacy of alternative therapies, such as cognitive behavioral and remediation therapy remains problematic (249). Cognitive remediation therapy show a neurobiological enhancing effect in patients with schizophrenia by increasing activations in several cerebral regions, specifically the frontal. Improved working memory and executive tasks in these patients was suggested to be in relation with post therapeutic neuroplasticity (250, 251). FMRI and PET studies comparing pre to post cognitive remediation therapy found increased brain activation in the frontal and parietal lobes, including the left medial frontal gyrus, the left inferior frontal gyrus, the right middle frontal gyrus, the right postcentral gyrus, and the inferior parietal lobule in patients with schizophrenia after therapy. Increased brain activity in medial and middle frontal gyrus in patients after therapy was related to the improvement in working memory performance (251). Cognitive remediation therapy has a significant association with improvement of psychosis symptoms and these effects remain at follow-up (252). Combined approaches using both computerized cognitive training and group therapy in schizophrenia patients show significant improvements in verbal memory and in symptom intensity (253). Cognitive training programs have shown little or non-significant effects on positive and negative symptoms in schizophrenia (254). Psychoeducation has been reported to reduce relapse and length of hospital stay. Additionally, it encourages medication compliance

(232). Cognitive behavior therapy has beneficial effect on positive symptoms (255). Additionally, it may attenuate brain responses to threatening stimuli and thus mediate symptom reduction in patients with schizophrenia (256). More evidence is needed to support other approaches such as social skills training (257).

Recently, consensus about the combination of pharmacological and psychosocial/cognitive therapies having more benefits for schizophrenia patients than one or the other individually has been reached (258, 259).

1.9 Neuroimaging findings

One of the most robust neuroanatomical findings in schizophrenia is enlargement of ventricles and related decreases in total brain volume and in cortical and subcortical tissue, which appear to be particularly pronounced in the prefrontal cortex, superior temporal cortex and hippocampal formation (260-264).

Schizophrenia is thought to be underpinned by neurodevelopmental abnormalities of brain gray matter and white matter function, structure and connectivity (191, 192, 265-268). Numerous brain regions have been implicated in the pathophysiology of this genetically and behaviorally complex disorder, suggesting that schizophrenia is not caused by any focal brain abnormality, but results from disturbed interactions between brain regions. In this regard, Friston and Frith (1995) have advanced that the core pathology of schizophrenia is an impaired neuromodulation of synaptic plasticity, leading to abnormal functional integration of neural systems (269).

Research evidence repeatedly demonstrated functional and structural alterations in cerebral gray matter (GM) and white matter (WM) in schizophrenia, particularly in the prefrontal cortex (including the anterior cingulate), the superior temporal gyrus, the limbic system (medial temporal lobe, hippocampus, entorhinal cortex, amygdala) as well as in the striatum, the insula, the thalamus and the cerebellum (50, 270-280).

Imaging studies demonstrate a large spectrum of inconsistent alterations associated with schizophrenia symptoms. GM losses in the orbitofrontal, medial prefrontal, lateral prefrontal and temporal cortices, thalamus, as well as limbic and subcortical structures were associated with negative symptoms. Conversely, positive symptoms were linked to the perisylvian regions and extended thalamic, superior temporal cortex GM losses. GM reductions in the temporal, insular

and medial prefrontal cortices, medial temporal and cerebellar regions was correlated with disorganized symptoms

2 Sex differences in schizophrenia

2.1 Epidemiology

Sex differences in schizophrenia have been reported in almost all facets of the disease: onset and course of the illness, clinical manifestation, treatment response, side effects of medication, cognitive and emotion deficits, social outcome, prognosis, comorbidities, genetics, in addition to cerebro-functional and morphological differences. Lewine's hypothesis stating the presence of sex differences in schizophrenia has been tested (281-285). A recent review of the literature by Van der werf and colleagues (2014) reported that overall males had a 1.15-fold greater risk of schizophrenia than females. Specifically, males had higher risk up until the age of 39, while females had higher risks between the ages of 50-70 (286). In addition, females had two incidence peaks of age, the first between 20 and 29 years, the second between 30 and 39 years; compared to males who had one incidence peak between the ages of 20-29 years. These finding suggest that sex differences are present in both incidence and risk of schizophrenia (27, 287). Okkels et al., (2013) found similar findings in a recent study on early onset schizophrenia; however, they report that higher male incidence than females in the periods 1971-1993 and 1971-2010. In the period 1994-2010 incidence rates were higher for females than males. They propose that changes in the diagnostic tools in recent years account for this finding (288). Anderson (2013) argued that, these time-periods coincided with a change in availability of data, with data from outpatient services only available in the latter time-period. These additional data may have partially contributed to the observed increase in incidence, and may have led to the narrowing of the sex differential, as males are more likely to be treated in an in-patient setting than females (289). Vanasse et al., (2012) conducted a population-based cohort study in Quebec using a population health services database between January 1996 and December 2006. They found that males were diagnosed at early ages while diagnosis in females was distributed in a uniform manner over age (290). This difference in prevalence was not reported in other studies (27, 291-293). In contrast, few studies have found higher incidences in females or no significant gender differences (294, 295) and no sex difference in terms of rates of mortality (26, 27).

2.2 Age of onset

Earlier age of onset in males compared to females is one of the most consistent finding in schizophrenia and later onset schizophrenia is reported in females (283, 286, 296-307). Meesters et al., (2012) performed a study on 100 males and 100 females unequivocally meeting DSM-III criteria for schizophrenia. The mean age at onset was about five years younger in males than in females. Approximately 9/10 males were diagnosed with schizophrenia before the age of 30 compared to only 2/3 of females. Late onset after the age of 35 years occurred in 17% of females and in only 2% of males (308). Several studies show that males usually develop the illness at age 18–25, while in females, the mean age of onset is 25–35 (301, 303). Similar to finding by Van der werf and colleagues (2014), females were found to have two periods during their life in which they may manifest a first onset: after menarche and after 40 years old (286, 291, 299, 300, 309, 310). These findings have also been replicated in first episode psychosis patients (311-313). Hafner et al., (1993), found that females at first onset were 3.2 to 4.1 years older than males (310). This sex difference disappears in the presence of family history (109, 299, 314).

Reduced estrogens after menopause may explain the increased prevalence in females over 40 (310, 315). In contrast, studies showing no sex difference in the age of onset were explained by the use of diagnostic criteria of DSM-III limiting the age to 45 and/or positive family history influencing the age of onset in both males and females equally (301, 305, 309, 310, 316-321). Several reports have found that even though age of onset is significantly earlier in males, no sex differences in the time from onset of symptoms to first hospitalization were found, suggesting that age of onset is related to biological rather than psychosocial factors (299, 322-324).

2.3 Premorbid history

Retrospective studies of patients and follow-up data of females with schizophrenia and their children show great premorbid deficits and more pronounced decline in males than females on several aspects of the illness. (303, 313, 325-335).

Males are more frequently diagnosed with substance abuse and antisocial behavior than females, while females have superior family and occupational function and superior clinical

responses (326). Males with schizophrenia have poorer premorbid functioning and more rapid deterioration than females especially when closer to the disease onset. Additionally male have significantly longer duration of untreated psychosis (DUP). Poor premorbid function was related to a more insidious onset and presence of negative symptoms, especially among males. Positive symptoms do not necessarily precede the onset (313). Males appear to have more severe negative symptoms and lower functioning than females and these differences are stable overtime (336). Poorer premorbid social adjustment is more common in male patients with primary persisting negative symptoms.(337). Males exhibit more severe premorbid impairment than females, however no sex differences were found in the decline of academic adjustment. Social dysfunctioning is spared in females until late adolescence (332, 338, 339). Several authors have suggested that these differences are due to the neuroprotective effects of estrogen (339-341) which might explain other sex differences, such as older age of onset, milder negative symptoms, and better response to antipsychotics (325, 342, 343).

Subgroups of patients with a good prognosis were characterized by: female sex, absence of premorbid deviant behavior and a high education level at first admission (344). These findings are consistent with findings that females with schizophrenia are more likely to be married and to have started a family at the time of first hospitalization compared to males schizophrenia (345). Males were reported to be more socially isolated, withdrawn, more likely to be single, have lower levels of education and work capacities (328, 346). It is suggested that enhanced premorbid functioning in females is due to later onset allowing them to complete their education, form personal relationships, marry and work before the manifestation of the illness (42, 301, 347). For example, Skokou and Gourzis (2014) found that earlier onset patients were characterized by significantly more single status, more avoidant premorbid personality disorder traits, and less passive-aggressive premorbid personality disorder traits, than late onset patients. Additionally, earlier age of onset seems to be associated with increased social inhibition and worse psychosocial adaptation in the premorbid period of paranoid schizophrenia (347). Males presented more schizoid-schizotypal traits before the first onset (348).

In summary, most studies show that females have better premorbid functioning than males (301, 313, 329, 344, 349-351). Few studies have reported no sex differences in premorbid function specifically at early stages of schizophrenia (352, 353). Worse premorbid functioning depended on age of onset and the presence of negative symptoms (352).

2.4 Birth complications

Obstetric complications (OCs) have been reported to appear more frequently in patients with schizophrenia relative to the general population. For example, O'Callaghan et al., (1992) reported that OCs were significantly more likely in patients with schizophrenia than in controls, in terms of number and severity. These finding were more significant in males that in females with schizophrenia, and were associated with a younger age at onset of their disease (354). These finding were also consistent with a subsequent study by Byrne et al., (2000) where males with earlier onset (before the age of 30) had a greater frequency and more severe OCs than the matched control group (355). In the same vein, Preti et al., (2000) found that severe obstetric complications were noted more often among males (41%) than among females (15%) (356). In addition, early-onset males were found to present more labor and delivery complications relative to controls and to female patients (357). The risk of schizophrenia following OCs was higher in males than in females, and OCs were more frequently associated with an early age at onset of schizophrenia in males (358-364).

The evidence that OCs increase the risk of subsequently developing schizophrenia is compelling, but we are still unclear about the antecedents of these OC. One hypothesis proposes that at least some OCs stem from the prenatal exposure to influenza. Thus, lower birth weight in patients with schizophrenia has been associated with exposure to influenza virus during the second trimester; patients' mothers were five times more likely to experience at least one definite OC in these cases (365-370). Nevertheless, the exact mechanism implicated in the relation between influenza, birth weight, and schizophrenia remains unclear (371). In addition to influenza, some authors propose that the maternal inflammatory response may be associated with fetal brain injury (372, 373). Others propose a maternal-fetal chronobiological dysfunction hypothesis to explain the relation between birth seasonality and schizophrenia, i.e. seasonal lack of sunlight is related to several thermo-chemical disturbances during the prenatal stage, that in turn affects the dopaminergic system in the fetal brain (hippocampus and striatum), leading to later development of schizophrenia (369, 374). Additionally, viral infections up to age 14 years were associated with higher risk of schizophrenia specifically in males (375). Some previous studies have reported that females exposed to influenza virus prenatally were more susceptible to developing schizophrenia than affective psychosis, however this relation was not observed in males, and the ratio of female:

male with schizophrenia increased with influenza exposure during the 5 months prior to birth (370, 376-378). Finally, maternal age at birth seems to plays a role in subsequent development of schizophrenia. A significant increase in risk of schizophrenia in males was related to mothers older than 39 years, and conversely in females with mothers younger than 19 years at the time of birth (358). Overall, despite the fact that numerous studies have investigated the relationship between OCs and schizophrenia, the findings remain somewhat inconsistent, mainly because of the variability of the reported birth complications, retrospective limitations, and small sample sizes (379).

2.5 Psychosocial factors

Psycho-socio-cultural factors play an important role in the perception and social outcomes of schizophrenia. Attempts to understand the implication of psycho-socio-cultural factors on schizophrenia patients' identity and role remain largely insufficient, specifically in relation with sex differences. Le Torre (1976) proposed gender identity and/or role problems as leading stressors in the diathesis-stress theory of schizophrenia, and that it is the only theory that accounts for the early onset of schizophrenia (380).

The role of each person is typically determined by her/his biological sex and depends on the cultural norms of each society. The use of the term "gender" interchangeably with term "sex" is a cause of important confusion. While "sex" refers to the biological and physical characteristics, "gender" on the other hand refers to masculine or feminine traits, behaviors, or beliefs as a psycho-socio-cultural attribution. Lewine (2004) found that sex, but not gender, was a significant predictor of age at first hospitalization, even when controlling for illness severity, Both sex and gender significantly contributed to the prediction of neuropsychological performance, beyond the contributions of education, age, and illness severity. (281).

A separate study examined sex and gender effects on seven domains of neuropsychological functioning in schizophrenia/schizoaffective patients and healthy individuals (284). The authors found main effects of sex on two neuropsychological domains and main effects of gender on five neuropsychological domains. Interestingly, executive functioning was unaffected by sex or gender, supporting its role as a behavioral marker of schizophrenia. Sajatovic et al., (2005), hypothesized

that subjectively, gender may affect the experience of illness in patients with schizophrenia in a way that may influence treatment and recovery, and that males and females with schizophrenia would have less identification with their traditional gender role characteristics. Their findings reveal that patients with schizophrenia experience their gender identity differently from what is expected by cultural norms. Both males and females with schizophrenia had lower masculine and feminine descriptive measures respectively in comparison to healthy controls. This has important implications on clinical recovery, as female patients tend to accept assistance from their families, a factor that improves schizophrenia outcomes; dependence on family is more gender-role-appropriate for females (381). The onset of schizophrenia typically occurs during late adolescence or young adulthood, coinciding with the period during which multiple levels of identity development normally occur. Because males may often develop the illness earlier in life compared with females, effects on gender identity among males with schizophrenia may be more profound than those among females (381). Several studies reported reversed gender role and identity in patients with schizophrenia (382-384).

Parrott and Lewine (2005) reported that higher parental socioeconomic status is associated with decreased symptom severity in female patients, but with increased symptom severity and decreased global functioning in males (385). This suggests that females from higher socioeconomic backgrounds are under less stress, and exhibit fewer and less severe symptoms of schizophrenia than those from lower socioeconomic standing. In contrast, in male patients, the higher the parental socioeconomic status, the more severely ill the patient is as judged by age at first hospital admission, symptoms, and global functioning. It seems that higher social status of origin may serve as a significant source of stress for males predisposed to schizophrenia. Males with schizophrenia from higher socioeconomic status face higher job expectations and greater stress due to difficulty fulfilling their high vocational expectations, while higher socioeconomic status appears to be a source of support for predisposed females. Similarly, Leung and Chue (2000), reported that families of males with schizophrenia were more critical, and expressed more emotion, and this had a greater negative impact on males in comparison to female patients (301). The most robust findings have been that males who presented an earlier onset of the disease were much less likely to be or had been married. In terms of social functioning, males with schizophrenia fared worse than females in several domains including self-care, daily activity, and work performance. The negative syndrome was correlated with greater role impairment, regardless of sex. Only females

presented a positive correlation positive symptoms and social role performance (386). Overall, psychosocial implications in schizophrenia remain relatively unexplored. A majority of studies show better social functioning in females with schizophrenia in comparison to males, but the issue of gender merits further investigation (387).

2.6 Clinical expression

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 (338, 388-396). Schizophrenia first presents with negative symptoms in 70% of cases, occurring two to six years before admission (309). Andreasen et al., (1990), found that schizophrenia patients with positive symptoms were mostly female, while patients who presented mixed and negative symptoms were predominantly males (89%) (389). Similarly Fenton & McGlashan (1991), found that male patients accounted for 60% of patients with high negative symptoms and female patients for 56% of those with low negative symptoms (388). Interestingly, no sex differences were found in positive or negative symptoms at hospital admission, however at follow-up, males had significantly more flat affect and anhedonia compared to female patients (36). Mayer et al., (1993) performed a retrospective study evaluating symptoms at admission and at discharge in patients with schizophrenia during the first manifestation of symptoms (397). Males were more apathetic at admission and discharge than females, and had higher depressive and psycho-organic syndrome scores at discharge.

Positive symptoms, have often been found equally in males and females with schizophrenia (398-401), more frequent in males (402) or more frequent in females (389, 403-409) who present more often affective symptoms, such as behavioral and sexual disinhibition, impulsivity, and other atypical psychotic symptoms (399, 403, 408). While negative symptoms seem to appear two to six years before admission, positive symptoms appear up to two years before (309). Marneros (1984) investigated the frequency of first rank symptoms (FRS) among schizophrenia patients at first hospitalization; females presented more thought insertion and hallucination symptoms relative to males who had other delusions of being influenced. Furthermore, females had more FRS at first hospitalization compared to males. Contrary to findings on the severity of negative symptoms in

males, no significant sex differences were found in the severity of positive symptoms (390, 407). In terms of frequency of positive symptoms, Morgan et al., (2008) investigated lifetime and current symptom profiles in males and females with schizophrenia. Their findings show that females were significantly less likely than males to report having hallucinations, delusions or poor concentration currently and more likely to report at least one serious episode of dysphoria over a lifetime (393).

In accordance to previous findings in the literature, Beratis et al., (1994) have found that mean age at onset was significantly higher in all female patients compared to males; this was especially true for the paranoid subtype (410). These findings were consistent with a subsequent report in Finnish schizophrenia patients who presented no sex differences in age of first admission, except for the paranoid schizophrenia where males had a significantly younger age at onset. In addition, females diagnosed with paranoid schizophrenia seemed to manifest the illness at an older age than males and females with other subtypes of schizophrenia (411). Other subtypes, such as disorganized schizophrenia have been shown in a few rare studies to appear earlier in females (410). 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 was particularly pronounces in males.(412).

Very few studies have addressed sex differences and subjective experiences of illness in schizophrenia. Thornicroft et al., (2002) found that males expressed more total needs and more unmet needs for 'accommodation', 'substance misuse', 'psychotic symptoms', 'harm to others', and 'sexual expression. In contrast, females expressed more total needs and more unmet needs in the domains of 'childcare' and 'harm to self' (413). Males 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 (390).

Several hypotheses have been offered to explain sex differences in symptom presentation in schizophrenia. One of the most widely accepted is the estrogen neuro-protective hypothesis, where estrogens, directly or indirectly, modulate symptom expression in males and females with schizophrenia. Organizational and activational effects have been attributed to sex hormones. Organizational effects occur in the brain during the prenatal fetal phase and are fixed, while activational effects fluctuate depending on the level of circulating hormones (311, 312, 315, 414-421). Seeman and Lang (1990) put forward several arguments in favor of the estrogen neuro-

protective hypothesis: The modulatory relation between the dopaminergic system and estrogens, delayed onset of illness of 4-6 years in females, males exhibiting one main peak of schizophrenia onset in their late teens and early twenties, females having an additional onset peak at age 40 to 45 years when estrogen levels decrease, less debilitating symptoms in females during the first decade following onset that thereafter approximates that of males particularly after menopause, lower doses of antipsychotic treatment effective premenopausally perhaps due to the potentiating effect of the antidopaminergic action of estrogen, and higher doses needed postmenopausally (417). Rendering further support to this hypothesis is the effectiveness of estrogen therapy in improving symptoms of schizophrenia (422, 423), the observed worsening of symptoms when estrogen levels drop sharply after pregnancy or during the follicular phase of the menstrual cycle (424, 425), and symptom improvement in females with schizophrenia during mid-luteal phase when estrogen levels are higher (426-429).

2.7 Course of illness

The course of illness is bound with the outcome. The term "outcome" refers to several domains in the life of a patient that go beyond the symptoms of the disease and considers the patient in a holistic manner. It includes quality of life, daily activities, severity of medication side effects, global functioning, employment, etc. (430-432). Morgan et al., (2008) investigated sex differences in outcomes and found that females were significantly more likely to be in long-term relationships and to have children, had better premorbid social functioning were more likely than males to be engaged in meaningful although not necessarily paid employment in the past twelve months, and were less likely to be on social aid (393). These findings are in agreement with those found previously (301, 325, 330, 403, 433, 434).

Generally, sex differences in outcome were found for both patients with schizophrenia and those with other psychotic disorders, with females consistently showing better functioning over time, recurrent episodes of remission, better global functioning, and fewer and shorter re-hospitalizations (330, 433, 435-437). No sex differences were reported when the duration of the illness exceeded 10 years (400, 438, 439). The sex differences in outcome for patients with schizophrenia are consistent over time (435). Grossman et al., (2008) analyzed their data 20 years

later, and found less psychotic symptoms for females during the course of illness and more improvement following 20 years; however, these trends were not observed in male patients. Not only females had a better clinical picture, but also they outperformed males in global functioning. In terms of recovery, 61% of females had a period of recovery compared to 41% of males during the course of 20 years (440).

The more favorable course of illness observed in females becomes lost with substance abuse (301, 441). Additionally, females are more likely to commit suicide during an acute exacerbation of the illness, although the rate of suicide is overall higher in males than in females (442, 443). This is likely due to the presence of more affective liability and affective symptoms in females than in males with schizophrenia (399, 403, 408, 442). Comorbid alcoholism and drug abuse may adversely influence the course of illness and is more prevalent among males than females with schizophrenia (292, 301, 442, 444). Schizophrenia patients have poorer outcomes compared to patients having other psychotic disorders additionally poorer outcomes are associated with longer follow-up periods (445).Male sex and pronounced negative symptoms were predictors for poorer outcomes (446). Lindamer et al., (2003) found that females with schizophrenia were older, many of them married and had medical insurance and presented less comorbidity with substance abuse than males. More females were living independently. In contrast, more male patients either were homeless or lived in assisted living establishments (447).

2.8 Cognition

Several studies have reported sex differences in cognitive performances in normal populations (448-452). These sex differences seem to be more prominent in schizophrenia patients. Cognitive impairments are present in both males and females with schizophrenia, but in varying degrees depending on the duration of the illness and the age of onset. Thus, some studies reported comparable cognitive deficits in male and female first episode patients (326, 453), but greater deficits in especially on verbal tasks, once the illness dated more than 5 years. Similar results were found for social cognition, Wisconsin Card Sorting Test, and verbal processing (454, 455). Schizophrenia patients performed worse than healthy subjects after matching for age and sex, and within patients, males performed worse than females (124, 455-458). Superior cognitive

performance in females seems to be consistent across other mental disorders, including bipolar disorder and schizotypal personality disorder (459, 460).

High quality studies have indicated that males and females with schizophrenia both have cognitive impairments but in different cognitive domains (453, 455, 459-463). Differential cognitive impairments were observed in female patients who had a significantly worse performance than female controls on attention, executive functions, visual memory, and motor functions, but not in language, verbal memory and visuospatial memory (455). More recent studies are in agreement reporting that females with schizophrenia have better performances in processing speed and episodic memory relative to male patients, while male patients perform better on visuospatial working memory (455, 461, 462). These differences in cognitive impairments may be a result of sex differences in age of onset or illness severity, and may become insignificant once these variables are controlled for (37, 403, 464-471).

Our group have investigated sexual dimorphism in 17 males and 17 female with schizophrenia during a task of episodic memory using event related potentials (ERP) (472). The two groups were matched for age, social economic status, education, and intelligence. In males, reaction times were modulated by valence, but in females, reaction times were mainly modulated by arousal. Accuracy was affected by both emotional valence and arousal in females, but not in males (472). Another study by our group addressed sexual dimorphism in strategic cognitive approaches (473). In this study, error types were analyzed during spatial working memory tests. No differences in number of errors were found, however, differences emerged in error and strategy profiles based on sex (473).

In 2007, our group started a series of studies investigating sex differences in schizophrenia. We presented preliminary behavioral data collected from 17 males and 13 females with schizophrenia during performance of a mental rotation task and from healthy subjects matched for age and sex (474). This task was specifically used for its already validated sensitivity to sex differences in healthy controls (451, 475-481). We found no significant difference between the two groups of females. In contrast, males with schizophrenia had a significantly longer reaction time and lower percentage of correct answers compared to male healthy controls. Thus, in schizophrenia female patients outperformed male patients in both reaction time and percentage for correct answers, while the opposite pattern is typically observed in the general population. Another recent study used the jittered orientation visual integration (JOVI) task - test of contour integration, which

activates orientation-selective feature detectors in the primary visual cortex and is used to evaluate early visual processing (482). Females demonstrated higher contour integration scores but lower performance on the context sensitivity index of presented shapes compared to males with schizophrenia. The findings suggest greater neurodevelopmental deficits in males with schizophrenia (483).

Few studies have reported better cognitive performance in males with schizophrenia (282, 285, 484). Lewine et al., (1996) found greater deficits on visual processing, verbal and spatial memory in females compared to males with schizophrenia (285). To date, cognitive impairments and their relation with sex differences in patients with schizophrenia remain inconclusive and merit further investigation (301, 485). A review by Mesholam-Gately et al., (2009) concluded that most studies addressing sex differences and cognition were not adequately designed to examine sex effects, contributing to the heterogeneity of cognitive performance reported in the literature (486). For more details please see our review paper in the appendix (487).

2.9 Treatment

Males and females with schizophrenia respond differently to treatment. Sex differences that affect drug response in schizophrenia include the following: delayed diagnosis in females, males presenting more deficit symptoms, stronger therapeutic alliance in females, males having more substance abuse and higher rates of smoking; females more often prescribed concomitant medications to treat comorbid problems, such as sleep disturbances, mood problems, endocrine disturbances, eating disorders, personality disorders (325, 434). Szymanski et al., (1995) found that females with first onset and chronic schizophrenia had similar response to treatments and that females had greater pharmacologic responsivity than males (405). In contrast, chronically ill males require twice as high a dose of psychotropic medication than females for effective maintenance (405, 488). Overall, males generally receive more neuroleptics compared to females, and have poor adherence to treatment (298, 489, 490).

Females with schizophrenia respond more quickly and show a greater degree of improvement on antipsychotic medications in comparison to males (405, 436, 491, 492). In addition, females have higher antipsychotic plasma levels in comparison to males after receiving

the same dose of drug, which may explain superior neuroleptic response and the need for lower doses of antipsychotics in females (493-496).

After menopause, females may require higher neuroleptic doses than males, and in turn may be more at risk for severe tardive dyskinesia, parkinsonian symptoms, and dystonia (301, 497, 498). In addition, females with schizophrenia are more likely to be prescribed antidepressants in comparison to male patients and more likely to change their antipsychotic treatment (499, 500). Rubin et al., (2008), also demonstrated better responsiveness to antipsychotic medication in females in relation to cognitive functions. The authors used cognitive tests that demonstrate sex differences in the general population, i.e. cognitive tests with scores that in normative studies favor males over females, such as visuo-spatial abilities, or favor females over males, such as verbal abilities. Their results revealed that females with schizophrenia had selective improvement on cognitive tests favoring females and decreased performances on cognitive tasks favoring males. In comparison, males seemed to have a worse performance than female patients on both types of tests (501).

Sex differences in treatment responses have been attributed to role of estrogen as a protective hormone against the illness in females and enhancing antipsychotic efficacy (417, 423, 502-505). Very few studies have investigated sex differences in relation to other therapeutic approaches, such as cognitive and behavioral therapy (CBT), cognitive remediation, psychoeducation and pharmacoeducation, social skill training and supported employment. To date, females with schizophrenia have shown more reductions in overall symptoms and increased insight using CBT in comparison to male patients, however more studies are needed to confirm these findings and to evaluate other approaches (506).

2.10 Structural neuroimaging findings

Sexual dimorphism has been observed in several brain regions in the general population (507-510). For example, regionally specific sex differences have been reported in regions associated with languages functions. Specially, females show larger volumes of the superior temporal cortex in proportion to the cerebrum (509). Moreover, age-related volume loss is greater in males than in females in the whole brain, specifically frontal and temporal lobes, whereas it is greater in females than males in the hippocampus and parietal lobes (510).

Gur et al., (2004) investigated sexual dimorphisms using MRI and automated tissue segmentation procedure to examine the orbitofrontal cortex and amygdala ratio (OAR) in males and females with schizophrenia (511). Male patients had reversed sexual dimorphism (increased OAR relative to healthy males) reflecting reduced amygdala volumes. The reverse pattern was found in female patients, where the decrease in OAR reflected reduced orbitofrontal volumes in comparison to female controls (511). A more recent study by Savadjiev et al., (2014) investigated normal brain pattern asymmetry referred to as torque in adolescent-onset patients with schizophrenia, using white matter geometry computation in diffusion tensor imaging data (512). This group observed a reversal of normal sexual dimorphism in white matter tissue in patients. These abnormalities were correlated with the severity of symptoms (512).

General Overview of Parenchymal Findings

It is now well established that morphological sex-related differences in the brain in healthy populations exist (510, 513-516). Imaging studies on sex–dependent brain abnormalities have consistently reported more severe disturbance in males than females with schizophrenia: reduced prefrontal volumes, reduced anterior temporal horn and medial temporal lobe volumes, more specifically amygdala, hippocampus, superior temporal and larger ventricular-brain ratios (VBR) (292, 301, 517-524). For example, Andreason et al., (1990) found that male patients had a smaller brain volume compared to controls in all four cortical regions, but not in the cerebellum; their CSF measures were higher than the controls' in relatively more anterior (rostral) regions, but not in occipital or cerebellar regions. The female patients, had a specific deficit in frontal lobe tissue only, as well as higher CSF measures in comparison with the controls in frontal and temporal regions and in the cerebellum (517). However, some studies have reported no sex differences (525-527). Gur et al., (1999) measured gray matter volumes (GMV) using the MRI scans of 130 patients (51 neuroleptic naive, 79 previously treated) and 130 healthy controls (75 males, 55 females in each group). They found that GMV displayed sex–dependent reductions, where male patients had a 6% reduction compared to 2% reduction in female patients. Results survived correction for age and total intracranial volume. In this study, only females with schizophrenia had a correlation between higher parenchymal volume and better premorbid functioning in females (513).

Subregional Findings

a) Brain volume, ventricular dilation, and cerebrospinal fluid

Ventricular dilation remains the most replicated and consistent in-vivo morphometric deficit observed in schizophrenia (528, 529). Clear relationships between ventricular dilation and clinical symptoms remain uncertain. Frontal and temporal lobe volume reductions have been the most frequently reported volumetric deficits (530). Sex differences in volume deficits have been equivocal, with some data suggesting that ventricular dilation is more prominent in male patients (518, 528). Nopoulos and colleagues (1997) reported a significant sex-by-diagnosis interaction for ventricular volume, such that males with schizophrenia had larger ventricles than healthy males, while no differences were observed between female groups (531).

Even when structural brain abnormalities are similar in males and females with schizophrenia, these abnormalities are generally more prominent in male patients. Molina and colleagues (2005) reported that only males with schizophrenia had significantly more CSF in the left prefrontal area, due to probable gray matter loss. Positive correlations between CSF values in the prefrontal and temporal regions and illness duration were found in males, but not in females with schizophrenia. These findings were observed only in the frontal and temporal regions and not in the whole hemisphere (532). Specific increases in sulcal and subarachnoid CSF appear prematurely in males with schizophrenia, while females with schizophrenia have aging effects similar to healthy subjects. Male patients, however, exhibited increased CSF even in young adulthood (533). Haijma et al., (2013) reported no sex differences with one major exception; the presence of reduced intracranial volume and significantly reduced white matter tissue volume in males with schizophrenia compared to healthy males. Intracranial volume reaches approximately 90% of its final volume at the age of 5 years and no further changes occur to its final volume after the age of 14. The more pronounced intracranial reductions in male patients may be attributed to a more severe or earlier neurodevelopmental derailment (534). Yotsutsuji et al., (2003) reported significant volume increases in the left temporal horn, the bilateral anterior horns, and the right ventricular body in male patients. Female patients had similar patterns of volume changes, but they were less significant (535). These findings suggest larger temporal gray matter reductions in males than females with schizophrenia.

Collinson et al., (2003) investigated hemispheric brain volume, asymmetry (torque) and IQ in early-onset schizophrenia patients. The authors found that total brain volume was significantly smaller in the group with early-onset disease relative to the control group (4.5%), especially in the

left hemisphere of female patients (6.0%). In addition a significant sex by diagnosis interaction was observed such that female patients had significantly reduced right more than left asymmetry relative to the female control group, while the male patients had decreased left more than right asymmetry relative to the female control group. In patients, these reductions in volume correlated with lower IQ measures (536).

b) Subcortical Temporal Lobe Deficits – Amygdala, Hippocampus, Hypothalamus

Bryant et al., (1999) reported smaller volumes in the superior temporal gyrus and the amygdala/hippocampal complex in patients compared to controls when male and female patients were grouped together. When patients were analyzed separately by sex, the left temporal lobe volume was significantly smaller in male patients compared to healthy males. In contrast, no significant differences were observed in the female groups (537).

Abnormalities of hippocampal morphology are another common observation in patients with schizophrenia (538, 539). With respect to sex effects on hippocampal volume, Irle et al., (2011) reported that only males with schizophrenia had hippocampal volume reduction in comparison with male controls. The authors also reported a correlation between smaller hippocampal sizes with longer duration of illness only in female patients. Female patients had normal hippocampal size at the onset of disorder, but after a few years, females and males with schizophrenia had similarly sized hippocampi (540). Additionally, female but not male first episode patients had significantly larger hippocampal volumes compared to female and male chronic patients (540). In contrast, Gur et al., (1998), Arciniegas et al., (1999), and others, reported that in minimally treated first-episode schizophrenia patients, significant sex by diagnosis effects were observed, with female patients having significantly smaller anterior and right hippocampal volumes than healthy control females. This effect was not observed in male patients suggesting that smaller hippocampal volumes are present even in early stages of the illness (541-543). Niu et al., (2004), found significantly, smaller volumes in the bilateral amygdala in males with schizophrenia compared to male controls. No differences in amygdala volume were observed between female groups. Between patient groups, females had a significant reduction in the right amygdala compared to males. A significant left-smaller-than-right volumetric asymmetry of the amygdala was detected only in male patients with schizophrenia (544). A left-right difference was only seen in the male patients, in whom significantly smaller left amygdala volume was observed (544).

c) Cortical and Gyral Deficits

Cortical gray matter volumes are frequently found to be reduced in schizophrenia (513, 545). Normal cortical patterns of sexual dimorphisms are disrupted in schizophrenia, in the frontomedial cortex, basal forebrain, cingulate and paracingulate gyri, posterior supramarginal gyrus, and temporal lobe (511, 546). Perturbation of normal gray matter volume asymmetry, has been observed in the left inferior parietal lobes in male patients, but not in female patients (547). No significant differences in gray matter asymmetry of volume were observed by Frederikse and colleagues (2000) in female patients compared to female controls, even when they had significantly smaller total brain volumes than healthy females (547). A recent study be Takayanagi et al., (2011) applied both volumetric and cortical thickness measures in MRI images. Consistent with the majority of structural findings in schizophrenia, patients in this study had gray matter volume reductions and cortical thinning in prefrontal and temporal cortices compared with controls. Sex differences were found in the bilateral amygdala, with more reductions in males than females with schizophrenia (548). Nesvag et al., (2008), found no significant effect of gender on variation in cortical thickness in their large-scale study (549). Sex differences in insular volume were reported by Duggal et al., (2005) in previously untreated patients with first-episode schizophrenia (550). The authors found that females with schizophrenia had significantly reduced right insular and anterior cingulate volume relative to healthy females. No difference between males with and without the diagnosis has been reported (551).

Takahashi, et al., (2002) investigated the anterior cingulate, a region anatomically associated with the corpus callosum. The authors found no significant group differences in the anterior cingulate volume in males; however, right anterior cingulate GMV was significantly reduced in the females with schizophrenia when compared with the healthy females. In addition, they lacked the normal structural asymmetry- right larger than left- in anterior cingulate gray and white matter volumes typically observed in female controls (552). Subsequently, Takahashi, et al., (2003) measured the volume of the perigenual cingulate gyrus in patients with schizophrenia and age and gender matched controls using MRI. Significant gender differences were found in the total gray and white matter volumes of the perigenual cingulate gyrus in control subjects where females had larger gray matter volumes than males (552). These gender differences were not significant in the patient group. Female patients also had significant decreased volumes of bilateral perigenual

cingulate gray matter compared with female controls, while no significant differences were observed between male groups (552). Male patients had volumetric reductions in prefrontal cortex, inferior parietal lobule, parahippocampus, and hippocampus (553). Significant differences in the covariance matrices in females and males with schizophrenia compared with healthy controls were observed in relationship with the inferior parietal and anterior cingulate gyri, the hippocampus and prefrontal cortex (553). The latter covariance was significantly associated with better verbal memory performance in females. In male patients, who had poorer performance compared to female patients, hippocampus and prefrontal cortex volumes were significantly correlated with memory performance (553). In healthy females, but not in males, the anterior cingulate was significantly correlated with memory performance. The authors suggested that females with schizophrenia compensate volumetric loss in the anterior cingulate by engaging alternative patterns between the inferior parietal and the prefrontal cortex (553). These findings were congruent with their previous study and with other reports (553, 554).

Narr et al., (2004) used MRI to measure 3D gyral complexity to investigate five cerebral regions in each hemisphere in patients with schizophrenia. The authors found a significant increase in cortical folding in the right superior frontal cortex in male patients compared to male controls. This difference was not observed in female groups, suggesting that these abnormalities predate illness onset and are of neurodevelopmental origin. These finding also suggest sexually dimorphic developmental processes that influence the organization of cortical folding probably during gyral formation in utero (555). In a subsequent investigation of the cingulate and occipital cortex, female patients had cortical thinning in cingulate and occipital regions bilaterally compared to healthy control females, while male patients had more cortical thinning in the left caudal anterior cingulate cortices, and in the paracentral lobule and posterior occipital regions bilaterally compared to male controls (554). In addition, male patients had small regional thickness increases in the gyrus rectus compared to male controls (554). Reports of reduction in the anterior cingulate volume in females with schizophrenia compared to control females contrasted with the absence of differences between male patients and comparison subjects (551).

Few studies have investigated the effect of sex on gyrification in schizophrenia (556-558). Only the study by Vogeley et al., (2000) found an effect of sex and diagnosis on the degree of gyral folding as assessed by gyrification index (GI). The study was conducted on postmortem brains of patients with schizophrenia and healthy controls using gyrification measures specifically in the

prefrontal region. The authors found a significant effect of diagnosis-by-sex interaction on the GI in the right prefrontal, where male patients had higher gyrification indices in comparison to healthy males, while no significant difference was observed in the female groups (558). The finding of sex differences in the GI in schizophrenia is consistent with several reports of more neuroanatomical abnormalities in males relative to female patients. For example, Narr et al. (2001) found a sex-by-diagnosis interaction in males with schizophrenia showing a greater loss of superior temporal sulcal slope asymmetry in the right hemisphere than females with schizophrenia. In addition, the authors found greater variability in the longitudinal fissure, reflecting both larger sulci and larger CSF space in male relative to female patients (559). In a different study, Bullmore et al., (1995), showed a global reduction in the right hemisphere radius of gyrification in males but not in females with schizophrenia (560). Similar structural sex differences have been found in volumetric and cortical thickness studies (20, 561-564). Highley et al., (2003) performed gyrification measures on frontal, temporal, parietal, and occipital regions in schizophrenia patients and age and sex-matched controls. The authors found no effect of diagnosis or sex on the degree of folding (565). In the present thesis, we investigate this issue further while considering sex, age, and illness duration effects.

d) Deep Brain Subcortical Gray Matter Deficits – Basal Ganglia, Thalamus

Sex effects on subcortical volumes remain equivocal. Arciniegas et al., (1999) found no significant diagnosis, hemisphere, or gender differences in thalamic volumes (543). Similarly, Gur et al., (1998) investigated basal ganglia and thalamus volumes in patients with schizophrenia and their relation to antipsychotic medication and severity of symptoms in patients with schizophrenia and healthy controls (542). The authors found that antipsychotic naïve male and female patients had lower thalamic volume, with no correlation between volumes and severity of negative symptoms, however higher volumes in the thalamus and the putamen were associated with more severe positive symptoms (542). Increased subcortical volumes in the putamen and globus pallidus were found equally in males and females with schizophrenia treated with antipsychotics (542).

e) Deep White Matter Deficits – Corpus Callosum

Abnormalities of the deep white matter, particularly in the callosal morphology, have been observed in schizophrenia. Narr and colleagues (2000, 2003, 2004, 2005, 2006, 2009) have conducted a series of studies investigating sex-dependent morphological abnormalities in schizophrenia (533, 554, 555, 566-568). Significant increases in maximum widths in anterior and posterior callosal regions in males with schizophrenia compared to male controls and increased patterns of callosal variability in female patients, without effects of diagnosis between female groups have been observed from imaging (567). Displacement and curvature increases were highly correlated with structural differences in surrounding neuroanatomical regions, including increased volume of the lateral ventricles (567). The authors suggest that females with schizophrenia are less vulnerable to ventricular enlargement and to alterations in surrounding neuroanatomic regions compared to male patients (567). Other less investigated regions is the cerebellum. Okugawa et al., (2003) found a significant cerebellar reduction in schizophrenia patients compared to controls, however no sex differences were found (569).

Sex-dependent structural differences and their relation with cognitive deficits have been addressed in few studies. For example Abbs et al., (2011) aimed at understanding why verbal memory processes seemed to be more preserved in females than males with schizophrenia by studying structural differences in prefrontal cortex, inferior parietal lobule, anterior cingulate gyrus, parahippocampus, and hippocampus (553).

3.0 Summary

Several hypotheses have been proposed to explain sex differences in the brain in schizophrenia. Crow (2008) suggested that sex differences related to psychosis are attributed to a genetic species-specific variation related to a locus on the X and Y chromosomes (570). Gene expression in this region is influenced by the degree of X and Y chromosomes pairing in male meiosis. This process is referred to as MSUC “meiotic suppression of unpaired chromosomes" which normally would lead to a more rapid mean rate of lateralization in females than in males and this in turn would relate to the higher incidence rate of language delays and dyslexias in males. This complex theory posits that language disturbances are integral to psychosis. Cerebral torque (in which the right frontal lobe is larger than the left, while the left occipito-temporo-parietal is larger than the right) is due to the development of neural connections associated with language. Disturbance in this neural development was proposed as the basis of the genetic predisposition to psychosis, and schizophrenia was proposed to be is a result of an abnormal cerebral lateralization associated with the emergence of language in humans (571). When this hypothesis is considered in the context of brain structures, it may explain the higher levels of anomalies found in male compared to female patients and the differences in the development of schizophrenia in males and females in general (572).

The influence of sex steroid hormones have also been suggested, particularly with respect to a putative neuroprotective effect of estrogen (573, 574). Estrogen is thought to influence sexual characteristics, the development of the brain aminergic networks, and the ability to adapt to stressful events, and to enhance the vulnerability threshold for psychosis by the downward regulation of dopamine. This model may explain the later onset and the more positive course of illness in females with schizophrenia. Increased levels of estrogen in females with schizophrenia with normal menstrual cycles were significantly associated with lower severity of schizophrenia symptoms suggesting that that estrogen had "a weak neuroleptic-like effect on schizophrenia symptoms" (325).

The accumulative body of neuroimaging findings remains, somewhat inconsistent and sometimes contradictory. Whether some of the inconsistencies with respect to sex differences in the published literature are associated with confounding factors, including duration of illness, age at onset of illness, ethnicity, IQ, and social status, methodological issues, imaging analyses

techniques remains unclear. Table X in the fourth article in the annex presents a summary of studies investigating sex differences in brain structure of schizophrenia patients. Given the variable findings in schizophrenia, it is evident that potential sex differences in this extremely complex mental illness are yet to be fully understood. In concordance with Dr. Shon Lewis' (1992) in his visionary paper *"Vive la Différence"* on the inherent difficulties in interpreting subtyping schizophrenia, we posit that "the advantage of using gender as the sub dividing variable by which to look for heterogeneity is that it is completely reliable, stable and valid- an immutable sociodemographic variable" (360).

4 Hypotheses and rationale

Hypotheses

We hypothesized to find significant sex differences in individuals diagnosed with schizophrenia in their morphology, symptoms, cognition, and emotion. In addition to the experimental work to test these hypotheses, a complete review of the literature was undertaken. The review led us to conclude that sex differences have been reported in almost all aspects of life of patients with schizophrenia. Given this state of affair, we performed a series of studies to shed light on several unresolved or unexplored areas in this field. Thus, in the first study we hypothesized that female patients will show less deficit than male patients (relative to the same-sex controls), that the gyrification index will show deterioration with age and duration of illness, and will be more pronounced in male schizophrenia patients. This hypothesis was based on several reports of more structural brain abnormalities in males than in females with a schizophrenia diagnosis. In the second study, we sought to assess the correlation between fronto-limbic volumes and schizophrenia symptoms. We hypothesized that correlations between symptoms, white and gray matter densities would show sex differences. In the final study, we predicted that male schizophrenia patients would show more cognitivo-emotional memory deficits, and that male patients would show more cerebral abnormalities in regions related to memory recall compared to female patients.

Rationale

The main goal of this thesis was to shed light on sex differences in schizophrenia. After a thorough review of the literature, we investigated the three cornerstones characterizing schizophrenia: symptoms, cognition, and emotion, using different morphological measures. Significant sex differences were revealed in all three domains no matter what methodological approach was used.

The approach taken was:

1- Assessment of gyrification from high-field MRI in males and females with schizophrenia
2- The investigation of the relationship between symptoms, cortical gray matter, deep brain white matter, and subcortical gray matter nuclei in males and females with schizophrenia.
3- The investigation of the relationship between cognitive capacity and gray/white matter morphology in males and females with schizophrenia.

5 Article 1

The following work has been accepted and published in *Clinical Schizophrenia & Related Psychoses* under the title: *"Sex, age and illness duration affect gyrification index in schizophrenia"* in Clin Schizophr Relat Psychoses. 2015 Jul 28. [Epub ahead of print] PubMed PMID: 26218234.

Despite well established cerebral sex differences in healthy population, only in recent years neuroimaging studies have addressed sex differences in schizophrenia as a possible explanation for discrepant findings. To examine potential sex differences in neuroanatomy, cognition, emotion, and schizophrenia symptoms we conducted a series of studies using divers imaging techniques. Only a few studies have investigated sex differences in schizophrenia using cortical measures. The first study of this doctoral thesis was designed to fill in this gap in the existing literature and it is one of the first to investigate sex differences using gyrification index (GI). Furthermore, we examined GI in relation to age and illness duration. Sex differences were revealed, showing that males with schizophrenia had more cortical alterations than female patients. An important and unanticipated finding was the fact that symptoms correlated only with the GI of the occipital lobe, despite the fact that abnormalities in GI in our group of schizophrenia patients in comparison to healthy controls were found in several cerebral regions.

Article 1

Sex, age, and illness duration affect gyrification index in schizophrenia

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Abstract

Introduction: The Gyrification Index (GI) represents the degree of cortical folding and is of special interest in schizophrenia, since alterations in cortical folding indirectly reflect white matter development and axonal connectivity underneath. To the best of our knowledge, only three studies have investigated the effect of sex on GI in schizophrenia. Differences in the GI between patients with schizophrenia and normal controls and the effects of sex, age, and duration of illness on the GI were investigated. **Methods:** T1 images were acquired from 48 schizophrenia patients (24 males [SZ-M] and 24 females [SZ-F]) and 48 healthy volunteers (24 males [NC-M] and 24 females [NC-F]) matched for age, sex, and handedness. Gyrification index analyses were performed using the fully automated CIVET pipeline. **Results:** Significantly lower GI were found in schizophrenia patients relative to normal controls in bilateral frontal, bilateral temporal, and bilateral parietal. Sex differences were found: lower GI in the right hemisphere in SZ-M relative to NC-M (no difference between female groups); GI values decrease with age in normal controls (with no sex difference) and in patients (SZ-M> SZ-F), with a more progressive deterioration in the right hemisphere in schizophrenia. Negative correlations were found between the duration of illness and the right parietal GI and the right occipital GI in SZ-M, and in the left frontal and bilateral temporal GI in SZ-F. Patients, regardless of sex, had positive correlations between negative symptoms and GI in the right occipital. SZ-M had negative correlations between the left occipital GI and negative symptoms, while SZ-F had positive correlations between negative symptoms and the right occipital GI. NC-F had greater GI values than SZ-F and male groups in the left frontal; greater values than both patient groups in the bilateral temporal and right frontal; and greater values in the left parietal compared to SZ-F. **Conclusion:** Since GI reflects, in part, alterations in cerebral development and connectivity, the decrease in GI observed in patients is in agreement with the neurodevelopmental model of disconnectivity in schizophrenia, in addition, we emphasize the importance of sex differences in schizophrenia.

Keywords: Schizophrenia, sex differences, magnetic resonance imaging, gyrification index, illness duration, age, symptoms.

1. Introduction

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

The Gyrification Index (GI) represents the degree of cortical folding by calculating the ratio of the entire inner cortical contour of the brain to that of the exposed outer surface contour. An increase in the GI index is thus correlated to an increase in the number and complexity of gyri (7). In 1991, Armstrong et al., (1995) stated that a change in this gyrification reflects aspects of the morphological development of the cortical layer (8). Developmentally, gyrification takes place following the completion of neuronal migration during the gestation period (9). The greatest increase in GI values occurs between 22 and 42 weeks of gestation (10). The gyrification index stabilizes shortly after birth and appears to be stable thereafter, even in the presence of atrophic processes affecting gray and white matter at a later age (10).

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

Few studies have attempted to investigate GI in schizophrenia patients (13-16) and those that did, focused mainly on the frontal lobe. These studies reported both greater (15, 17) and lower gyral complexity (18, 19). A study by Sallet et al., (2003) and Palaniyappan et al., (2011) reported global reductions but with fluctuating regional increases in right anterior prefrontal cortex and bilateral

frontomarginal regions (20, 21). Harris et al., (2004) compared a larger sample (N=34) of first-episode patients to healthy controls (N=36) and assessed the prefrontal, temporal, parietal, and occipital lobes. The authors found a trend toward reduction in the left prefrontal region but significant increases were observed in the right temporal regions (15). These structural abnormalities may provide insight into differences in schizophrenia symptoms (14, 20, 22).

There is a paucity of investigating the effect of sex on GI measures in schizophrenia (20, 23, 24). Only the study by Vogeley et al., (2000) found an effect of sex and diagnosis on the degree of gyral folding. Vogeley et al., (2000) conducted the study on postmortem brains of patients with schizophrenia (N=24) and healthy controls (N=24) using gyrification measures specifically in the prefrontal region. The authors found a significant effect of diagnosis-by-sex interaction on the GI in the right prefrontal, where male patients had higher gyrification indices in comparison to healthy men, while no significant differences were observed in the female groups (24). The second study by Highley et al., (2003), performed gyrification measures on frontal, temporal, parietal, and occipital regions in 61 patients with schizophrenia in comparison with 42 healthy controls (21 females). The authors found no effect of diagnosis or sex on the degree of folding (25). Bonnici et al., (2007) used an automated gyrification measure in the frontal lobe to compare schizophrenia patients (14 males and 11 females) and patients with mental retardation and healthy controls. Schizophrenia patients had reduced gyrification; however, the authors report no significant effect of sex on gyrification index (13). Similarly Cachia et al., (2008) investigated local sulcal index in schizophrenia patients (10 females and 20 males) with hallucination in comparison with healthy controls. Reductions were significant in the superior temporal sulcus bilaterally, in the left middle frontal sulcus with no significant main effect of sex on the results (22).

More recently Palaniyappan et Liddle (2012) performed gyrification analyses in a group of 57 schizophrenia patients (50 males), and a second time after exclusion of the 7 female subjects. The authors report reductions in the left insula, the superior temporal gyrus, the caudal superior temporal and inferior parietal regions. Exclusion of the female subjects did not change the results. The authors recommended caution in the interpretation of these results and pointed out the need for studies with equal male/female ratios (26).

The aim of the present study was three-fold: 1) to investigate differences in the GI between patients with schizophrenia and normal controls; 2) to investigate the main effects of sex on the GI in larger samples of patients; and 3) to investigate the main effects of age and duration of illness

on the GI. Based on previous studies, we hypothesized that: 1) patients would have lower GI than normal controls; and 2) female patients would show less GI deficit than male patients (relative to the same-sex controls). This hypothesis is based on several reports of more structural brain abnormalities in males than in females with a schizophrenia diagnosis (27-32). It is also expected that 1) the GI will show deterioration with age, which will be more pronounced in schizophrenia patients, and 2) the duration of illness will be associated with lower GI.

2. METHODS

2.1 Participants

Ninety-six subjects were included in the present study. Inclusion criteria for the schizophrenia group were a DSM-IV (33) diagnosis of schizophrenia with no medical or neurological diseases and no concomitant axis-I or axis-II disorders. Forty-eight schizophrenia patients (24 males [SZ-M] and 24 females [SZ-F]) and 48 normal controls (24 males [NC-M] and 24 females [NC-F]) participated in the study after signing a detailed informed consent approved by the local scientific and ethics committees.

SZ and NC were matched for age, sex, and handedness (34) (SZ-M: mean=31.25 years, SD=7.97; NC-M: 33.50 years, SD=8.69; p=.355; df=46 and SZ-F: mean=33.04 years, SD=8.38; NC-F: 29.92, SD=7.15, p=.171; df=46). No differences between groups were found in the parental socio-educational status (SZ-M: mean=2.82, SD=0.61; NC-M: mean=2.32, SD=1.12, df=46; SZ-F: mean=2.63, SD=1.06; NC-F: mean=2.18, SD=1.13, p=.183; df=46) as assessed by the National Occupational Classification (NOC) (35) on a scale ranging from 1 to 4. There were no significant differences between male and female patients in either mean duration of illness or dose of antipsychotic medication in chlorpromazine equivalence. Patients were stabilized on one or more atypical antipsychotic. The effects of antipsychotic medications on GI were considered through estimation of chlorpromazine dose equivalents (36). Patients with DSM-IV (33) criteria of affective, schizoaffective and schizophreniform psychoses as well as patients with past or present neurological or Axis-I psychiatric disorder, alcoholism or drug abuse were excluded from the study. Control participants were screened with the non-patients edition of Clinical Interview for DSM-IV [SCID] (37). Symptoms severity was rated according to the positive and negative syndrome scale [PANSS] (38). Handedness was evaluated with the Edinburgh Inventory (34)

(Table 1). 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 as bipolar disorder, personality disorder, etc.; therefore, a psychiatric consultation favors a better diagnosis.

- Insert Table 1 just about here -

2.2. Magnetic Resonance Imaging Acquisition.

Individual high-resolution co-planar anatomical images were acquired using an 12channel 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. Magnetic Resonance Imaging Analysis.

2.3.1. Gyrification index preprocessing

Gyrification index analyses were done using the fully automated CIVET pipeline. For details, please see following references (39-44) and the following link http://www.nitrc.org/plugins/mwiki/index.php/neurobureau:CIVETPipeline.

2.3.2. Gyrification index measurement

An intermediate cortical surface, halfway between the inner and outer CLASP (Constrained Laplacian Anatomic Segmentation using Proximity) surfaces, was used for measuring the surface morphometrics as it represents a relatively unbiased representation of both sulcal and gyral regions (45). The cortical area was calculated in the whole hemisphere and each lobar region by summing the Voronoi area based on geodesic distances over the folded topology of the surface (46). The middle cortical surface was divided into the sulcal and gyral regions by thresholding the depth map, i.e. 3D Euclidean distance from each vertex to the nearest voxel on the convex hull volume (47). The threshold of the depth map was determined from the fact that the human cerebral cortex is a highly folded sheet with 60–70% of its surface area buried within folds (7, 48). The mean GI was

defined as the ratio between the total surface area and the superficially exposed surface areas such as the gyral regions in each hemisphere and lobe (7). Please see figure 5 as an example.

-----Insert Figure 5 around here -------

2.4. Statistical Methods and Analysis.

The unified statistical approach to deformation-based morphometry was applied to the cortical surface (49), which is specifically performed when using age and gender as covariates. The cerebral cortex has the topology of a 2D highly convoluted sheet. As the brain develops over time, the cortical surface area, thickness, curvature, and total GM volume change. It is highly likely that such age-related surface changes are not uniform. By measuring how such surface metrics change over time, the regions of the most rapid structural changes can be localized. We avoided using surface flattening, which distorts the inherent geometry of the cortex in our analysis and is only used in visualization. To increase the signal to noise ratio (SNR), diffusion smoothing, which generalizes Gaussian kernel smoothing to an arbitrary curved cortical surface, has been developed and applied to surface data (2D smoothing). As an illustration, Evans and colleagues have demonstrated how this new surface-based morphometry can be applied in localizing the cortical regions of the gray matter tissue growth and loss in the brain images longitudinally collected in the group of children and adolescents. Further studies stated that each of the segmentation, thickness computation, and surface registration procedures are expected to introduce noise in the thickness measure (50, 51). To counteract this, data smoothing was used to increase the signal-to-noise ratio (SNR), and the sensitivity of statistical analysis. For analyzing data in 3D whole brain images, Gaussian kernel smoothing is widely used, which weights neighboring observations according to their 3D Euclidean distance. In the present study, however, the data lie on a 2D surface so the smoothing must be weighted according to distance along the surface. This method is adopted to reduce the noise in the thickness measure especially when co-varying with age and gender. Diffusion smoothing, that smooths data on an explicit 2D cortical surface representation, is based on the observation that, in Euclidean space, Gaussian kernel smoothing is equivalent to solving an isotropic diffusion equation. This diffusion equation can also be used on the surface manifold to increase the SNR. This is done to reduce noise and to overcome problems caused by neuroanatomic variability within the gender and age groups. In addition, mixed model regressions to account for

missing data, irregular intervals between measurements, and within-person correlation, were used to examine the developmental trajectories (52). The threshold for statistical significance was set at an α of 0.05. Correction for multiple comparisons was needed to control the false-positive rate. All statistical thresholds were determined by application of the false discovery rate (FDR) technique controlling procedure for multiple comparisons. This approach is reported to be effective for the analysis of neuroimaging data (53).

A factor analysis (or 'diagnostic group') of diagnosis-x-gender was performed, for variables revealing significance for the GI. Then analysis of covariance with mean GI as the dependent variable with separate analyses for the left and right hemispheric, in addition to each lobe GI, were performed according to general linear model corrected for multiple comparisons. A series of univariate ANOVAs were subsequently performed according to the general linear model. Regression analyses were also performed, using GI as the dependent variable and age, symptoms scores and duration of illness as regressors. Potential interactions between regressors and diagnosis and sex were tested. Analyses were performed using the SPSS 17 software. Type I error was controlled by adopting Bonferroni corrections at $p<0.05$.

3. Results

3.1 Psychiatric assessments

Independent t-tests revealed a significant difference in negative and total PANSS scores and age of onset between males and females with schizophrenia, but no differences were found in medication or illness duration (Table 1).

---Insert Table 1 about here -----

3.2. Gyrification index

3.2.1: Results by hemisphere

The t-test revealed a significant main effect of group on the right hemisphere GI ($t=2.723$, $p=.008$) and the left hemisphere GI ($t=2.127$, $p=.037$), such that the patient group exhibited a lower GI compared to the control group. Based on previous findings, second level ANOVA was performed on the female and male groups separately. There was a significant main effect of group

in males on the right hemisphere GI (t=2.545, p=.018), and only a trend on the left hemisphere GI (t=1.947, p=.058), where SZ-M had a significantly lower GI compared to control males. No main effect of group was observed in females.

3.2.2. Regression and general linear model Analyses with hemispheres

General linear Model regression in SPSS revealed a Group-by-Age interaction in the GI of the right (F (1,95)=2.221, p0.019, df=94) and the left hemisphere (F (1,95)=2.239, p=0.018, df=94), such that the diagnosis of schizophrenia affected the rate of GI loss with age. The direction of this interaction was such that increased age correlated with lower GI in the right hemisphere and in the left hemisphere GI (Figure 1a and 1b) with more rapid decrease in GI bilaterally with progressive age in the patient group compared to controls.

The examination of patients, revealed an Age x Sex interaction in the right and left hemisphere GI showing that males with schizophrenia had greater GI reductions bilaterally yet more pronounced in the right hemisphere with progressive age compared to females with schizophrenia (Figure 2a and 2b). Furthermore, an interaction was observed between duration of illness and sex demonstrating a greater decrease in GI in the right hemisphere with the duration of illness only in males with schizophrenia (Figure 4). There were no significant correlations found between hemispheric GI and symptoms in either group or patients.

- Insert Figure 1a, and Figure 1b just about here -

- Insert Figure 2a, and Figure 2b just about here -

- Insert Figure 3 just about here –

3.2.3 Results by Lobe

The t-test performed between patients and controls revealed significant differences in the left frontal lobe GI (t=3.358, p=.001, df=94), the left temporal (t=2.902;p=0.005, df=94) and the left parietal GI (t=2.596; p=0.011, df=94), the right frontal lobe GI (t=2.886, p=0.005, df=94), the right temporal lobe GI (t=3.672; p=0.001, df=94) and the right parietal lobe GI (t=2.198; p=0.030, df=94), such that the patient group exhibited lower GI compared to the control group. ANOVAs were performed for the 4 groups NC-M, SZ-M, NC-F and SZ-F. Differences between groups were significant in the left frontal (F (1,95)=6.949; p=0.001, df=92) where NC-F had higher GI than NC-

M (p=0.030), SZ-M (p=0.001) and SZ-F (p=0.004, df=92); and in the left temporal (F (1,95)=3.924; p=0.011, df=92) where NC-F had higher GI than SZ-M (p=0.034) and SZ-F (p=0.016); in the left parietal (F (1,95)=0.021; p=0.023, df=92), where NC-F had higher GI than SZ-F (p=0.023); in the right frontal (F (1,95)=5.165, p=0.002, df=92), where NC-F had higher GI compared to SZ-M (p=0.001) and SZ-F (p=0.046); in the right temporal (F (1,95)=6.263; p=0.001, df=92), where NC-F had higher GI than SZ-M (p=0.01) and SZ-F (p=0.001) (Figure 4).

----------Insert Table 2 and Figure 4 about here----------

3.2.4 Regression Analyses with lobes

Regression analyses revealed a negative correlation between the duration of illness and the right parietal GI (r^2=0.166; β=-0.407; t=-2.092; p=0.048, df=46) and the right occipital GI (r^2=0.183; β=-0.427; t=-2.218; p=0.037, df=46) such that male patients show more rapid decrease in GI. While females had more rapid decrease in the left frontal GI (r^2=0.306; β=-0.553; t=-3.115; p=0.005, df=46), the left temporal GI (r^2=0.211; β=-0.459; t=-2.422; p=0.024, df=46) and the right temporal GI (r^2=0.280; β=-0.529; t=-2.927; p=0.008, df=46).

Regression analyses between symptoms and GI performed in patients regardless of sex revealed positive correlations between negative symptoms and the right occipital GI (r^2=0.170; β=0.398; t=3.064; p=0.004, df=46). SZ-M had negative correlations in the left occipital GI with negative symptoms (r^2=0.221; β=-0.470; t=-2.495; p=0.021, df=46), while SZ-F had positive correlations between negative symptoms and the right occipital GI (r^2=0.230; β=0.479; t=2.561; p=0.018, df=46).

4. Discussion

The main findings of the present study are: (1) Significant lower values of the overall GI and in individual lobes in schizophrenia patients relative to normal controls; (2) Significant lower values of the GI in the right hemisphere in schizophrenia males relative to the same-sex controls (no difference between female groups); (3) GI values decrease with age in healthy controls (with no sex difference) and in patients (greater in males than in females), with a more progressive deterioration in the right hemisphere in schizophrenia; (4) Significant GI values decrease with the

duration of illness in schizophrenia males but not in schizophrenia females; (5) Patients having significantly lower GI in bilateral frontal, bilateral temporal and bilateral parietal compared to controls; (6) Female controls having greater GI values than schizophrenia females and both male groups in the left frontal; greater values than both patient groups in the bilateral temporal and right frontal; and greater values in the left parietal compared to females with schizophrenia. (7) An inverse correlation between the duration of illness and the right parietal GI and right occipital GI in male patients; (8) Female patients having a negative correlation between the duration of illness and the left frontal and bilateral temporal GI; (9) In all patients, positive correlations between negative symptoms and GI in the right occipital; (10) Male patients having inverse correlations in the left occipital GI with negative symptoms; (11) Female patients having positive correlations between negative symptoms and the right occipital GI.

These findings point to abnormalities in the morphological development of the cortical layer in schizophrenia. These alterations were generalized bilaterally in the frontal, temporal, and parietal cortices, and were in concordance with previous structural findings in the literature (22, 54, 55). Taking into consideration two facts: (i) GI values reach their maximum during the first years of life and decrease gradually during childhood; (ii) the gyrification pattern is mostly completed at birth, yet, the sulco-gyral folds continue to develop until early adulthood (10), we advance that neurodevelopmental brain changes may be present at the onset of the illness (27, 32, 56-61) with further changes occurring during progression of schizophrenia (56, 62-65) specifically in males (56, 66). The finding of sex difference in the GI in schizophrenia is consistent with several reports of more neuroanatomical abnormalities in male relative to female patients. For example, Narr et al., (2001) found a Sex-by-Diagnosis interaction with schizophrenia males showing a greater loss of superior temporal sulcal slope asymmetry in the right hemisphere than schizophrenia females. In addition, the authors found greater variability in the longitudinal fissure, reflecting both larger sulci and larger CSF space in male relative to female patients (67). In a different study, Bullmore et al., (1995) showed a global reduction in the right hemisphere radius of gyrification in males but not in females with schizophrenia (30). Similar structural sex differences have been found in volumetric and cortical thickness studies (27-29, 31, 32).

In addition to sex difference in the GI in schizophrenia, we have found a significant decrease in GI values with the duration of illness. Decreases were also seen in the right parietal and right occipital lobes in males. Female patients had decreases mostly in the left hemisphere (left frontal

and temporal and right temporal). Several studies have shown a progressive decrease in global brain measurements associated with illness duration (68, 69), specifically in frontal (70, 71) and temporal lobes (68, 70), however, the present study is, to the best of our knowledge, the first report of sex differences in GI taking into consideration the duration of illness.

The overt clinical expression of some psychiatric and neurodevelopmental disorders may be a reflection of an underlying abnormality in growth of cortical convolutions (72). It is plausible that the significant decrease in the GI observed in schizophrenia is related to the disease itself. Nevertheless, we found only an association between occipital GI and negative symptoms, in addition there were sex differences, where female patients with more negative symptoms also had greater GI in the right occipital cortex, and male patients who had greater negative symptoms had lower GI in the left occipital cortex. A study by Onitsuka et al., (2007) showed a relationship between reduced volumes in the visual association areas and hallucinations. Their study included only male schizophrenia patients (73). Bijanki et al., (2015) reported an association between increased white matter fractional anisotropy in the occipital lobe and increased score of Scale for the Assessment of Negative Symptoms (SANS) in schizophrenia patients. The authors did not report any sex differences (74). Of relevance is a study by Mitelman et al., (2003) showing that patients with negative symptoms and poorer outcomes had significantly lower gray matter volumes in the temporal and occipital lobes compared to better outcome patients and healthy controls (75).

The abnormalities in GI in our group of schizophrenia patients in comparison to healthy controls were not the same regions that correlated with schizophrenia clinical symptoms as measured by the PANSS. We postulate that cognitive deficits play a role in such discrepancy. Several studies have shown abnormalities in these regions in relation with deficits in mental rotation abilities (76) IQ performance (77) language processing (78), and face recognition (79). Along this line of evidence, Jou et al., (2005) demonstrated abnormalities in cortical gyrification in individuals at increased genetic risk of schizophrenia (i.e., not presenting the full schizophrenia symptomatology) (80).

Interestingly, female controls had greater GI values than schizophrenia females and both male groups in the left frontal; greater values than both patient groups in the bilateral temporal and right frontal; and greater values in the left parietal compared to females with schizophrenia. Luders et al., (2006) reported similar findings. In this study, the authors found increased gyrification in frontal, parietal, temporal, and occipital regions in healthy females compared to healthy males (81).

While previous findings investigating GI in schizophrenia (20, 23, 24) did not find any significant sex difference, in our study, decreased GI was observed in different regions in schizophrenia males relative to control males, and in females with schizophrenia compared to control females. Furthermore, sex differences were observed in regions showing lower GI in association age as well as illness duration, which in itself, suggest a differential neuropathological process implicated in male and female patients. Palaniyappan et al., (2011) showed a strong negative correlation between age and gyrification index in schizophrenia in general without reference to sex, suggesting a higher degree of age related morphometric changes in patients (26). Several hypotheses have been proposed to explain sex differences in the schizophrenia brain. Crow et al. (2008) suggested that sex differences related to psychosis are attributed to a genetic species-specific variation related to a locus on the X and Y chromosomes (82). Gene expression in this region is influenced by the degree of X and Y chromosomes pairing in male meiosis. This process is referred to as MSUC “meiotic suppression of unpaired chromosomes" which normally would lead to a more rapid mean rate of lateralization in females than in males and would in turn, relate to the higher incidence rate of language delays and dyslexias in males (82). This complex theory posits that language disturbances are integral to psychosis. Cerebral torque (where the right frontal lobe is larger than the left, while the left occipito-temporo-parietal is larger than the right) is due to the development of neural connections associated with language: from right to left in relation to the motor speech output and from left to right in relation to speech perception. Disturbance in this neural development was proposed as the basis of the genetic predisposition to psychosis, i.e. the authors suggest that schizophrenia is a result of an abnormal cerebral lateralization associated with the emergence of language in humans. When this hypothesis is considered in the context of brain structures, it may explain the higher levels of anomalies found in male compared to female patients in our study and the differences in the development of schizophrenia in males and females in general (83). The influence of sex steroid hormones has also been considered in a few studies (84, 85). These studies strongly suggest that the neuroprotective effects of estrogen (which influences sexual characteristics, development of the brain aminergic networks, and the ability to adapt to stressful events) enhance the vulnerability threshold for psychosis by the downward regulation of dopamine. Such mechanism may explain the later onset and the more positive course of female schizophrenia. In this vein, an amalgam of research has been proposed to explain the presence of significant brain structure abnormalities in schizophrenia males in comparison to normal control

males and schizophrenia females, such as greater enlargement of the lateral and third ventricles and decreased frontal and temporal lobe volumes (86, 87) and disease progression (88-90). With regards to the latter, Riecher-Rossler et al.,(1994) and Hafner (2003) found that increased levels of estrogen in females with schizophrenia with normal menstrual cycles were significantly associated with lower severity of schizophrenia symptoms suggesting that that estrogen had: "a weak neuroleptic-like effect on schizophrenia symptoms"(89, 91, 92).

Because cortical gyrification is an important marker of cerebral development (10), we investigated the relationship between GI and age in our 96 subjects. We found a more pronounced decrease in GI with age in schizophrenia patients relative to healthy controls. Cortical convolution is influenced by the degree of thalamo-cortical connections (11). Hence, it is interesting to note the significant negative correlation between the GI and the duration of illness. Indeed, various studies have implicated thalamo-cortical connections in the pathophysiology of schizophrenia (93-95). Based on the preceding arguments, we suggest that the inverse correlations observed in the present study reflects the long-term instability in information processing and the failure of associative mental processes across the years of illness in schizophrenia.

This study is limited by the use of the GI only. Further studies should investigate GI along with cortical thickness in order to have a better estimate of gray matter density. We emphasize that our results are preliminary and that larger studies are necessary to confirm our findings. Notwithstanding these limitations, there are two major differences between the present technique and other contemporary image analysis methods, which add to our confidence in interpreting the data: first, we used a completely automated method to assess GI. An advantage of an automated method is that rater error is not a factor and is corrected for multiple threshold. Second, we first used the MNI_AutoReg, which performs a 9-parameter, linear registration to the registration target model in order to later bring native (original raw) images into MNI-Talairach space. Then, during the 16th stage of the Civet pipeline 'non-linear surface registration' stages, where the cortical surfaces are produced, they need to be aligned with the surfaces of other brains in the data set so that cortical morphology data can compared across subjects. Following this Surfreg performs a non-linear registration of the surfaces to a pre-defined template surface. These steps are crucial to resampling in native space, which is essential when working with schizophrenia brains. Note that while the vertices have been aligned, the topological measurements associated with them (e.g. GI), remain unchanged in this process. Finally as gyrification decreases in both healthy controls and

patients, gyrification thus becomes a much more ambiguous marker as it is difficult to isolate factors of gyrification decline with healthy aging and even more so with disease (confounded by disease progression, different behavioural factors, and substance/medication exposure). For instance, future research capturing cortical folding measures prior to or at the time of disease onset may help clarify what brain effects are due to early development versus secondary effects of disease.

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

References

1. Gur RE, Keshavan MS, Lawrie SM. Deconstructing psychosis with human brain imaging. Schizophr Bull. 2007;33(4):921-31.

2. Girbau D. A neurocognitive approach to the study of private speech. Span J Psychol. 2007;10(1):41-51.

3. Lawrie SM, Abukmeil SS. Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. Br J Psychiatry. 1998;172:110-20.

4. Gunther W. MRI-SPECT and PET-EEG findings on brain dysfunction in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 1992;16(4):445-62.

5. Friston KJ, Frith CD. Schizophrenia: a disconnection syndrome? Clin Neurosci. 1995;3(2):89-97.

6. Van Essen DC. A tension-based theory of morphogenesis and compact wiring in the central nervous system. Nature. 1997;385(6614):313-8.

7. Zilles K, Armstrong E, Schleicher A, Kretschmann HJ. The human pattern of gyrification in the cerebral cortex. Anat Embryol (Berl). 1988;179(2):173-9.

8. Armstrong E, Curtis M, Buxhoeveden DP, Fregoe C, Zilles K, Casanova MF, et al. Cortical gyrification in the rhesus monkey: a test of the mechanical folding hypothesis. Cereb Cortex. 1991;1(5):426-32.

9. Richman DP, Stewart RM, Hutchinson JW, Caviness JVS. Developmental model of brain convolutional development. Science 1975;189 (4196):18-21.

10. Armstrong E, Schleicher A, Omran H, Curtis M, Zilles K. The ontogeny of human gyrification. Cereb Cortex. 1995;5(1):56-63.

11. Rakic P. Defects of neuronal migration and the pathogenesis of cortical malformations. Prog Brain Res. 1988;73:15-37.

12. Armstrong E, Schleicher, A.,Zilles, K. . Cortical folding and the evolution of the human brain. J Hum Evol 1993;25 387-92.

13. Bonnici HM, William T, Moorhead J, Stanfield AC, Harris JM, Owens DG, et al. Pre-frontal lobe gyrification index in schizophrenia, mental retardation and comorbid groups: an automated study. Neuroimage. 2007;35(2):648-54.

14. Harris JM, Whalley H, Yates S, Miller P, Johnstone EC, Lawrie SM. Abnormal cortical folding in high-risk individuals: a predictor of the development of schizophrenia? Biol Psychiatry. 2004;56(3):182-9.

15. Harris JM, Yates S, Miller P, Best JJ, Johnstone EC, Lawrie SM. Gyrification in first-episode schizophrenia: a morphometric study. Biol Psychiatry. 2004;55(2):141-7.

16. Palaniyappan L, Mallikarjun P, Joseph V, White TP, Liddle PF. Folding of the prefrontal cortex in schizophrenia: regional differences in gyrification. Biol Psychiatry. 2011;69(10):974-9.

17. Vogeley K, Tepest R, Pfeiffer U, Schneider-Axmann T, Maier W, Honer WG, et al. Right frontal hypergyria differentiation in affected and unaffected siblings from families multiply affected with schizophrenia: a morphometric mri study. Am J Psychiatry. 2001;158(3):494-6.

18. Kulynych JJ, Luevano LF, Jones DW, Weinberger DR. Cortical abnormality in schizophrenia: an in vivo application of the gyrification index. Biol Psychiatry. 1997;41(10):995-9.

19. Harris JM, Moorhead TW, Miller P, McIntosh AM, Bonnici HM, Owens DG, et al. Increased prefrontal gyrification in a large high-risk cohort characterizes those who develop schizophrenia and reflects abnormal prefrontal development. Biol Psychiatry. 2007;62(7):722-9.

20. Sallet PC, Elkis H, Alves TM, Oliveira JR, Sassi E, Campi de Castro C, et al. Reduced cortical folding in schizophrenia: an MRI morphometric study. Am J Psychiatry. 2003;160(9):1606-13.

21. Palaniyappan L, Mallikarjun P, Joseph V, White TP, Liddle PF. Folding of the prefrontal cortex in schizophrenia: regional differences in gyrification. Biol Psychiatry. 2011;69(10):974-9.

22. Cachia A, Paillere-Martinot ML, Galinowski A, Januel D, de Beaurepaire R, Bellivier F, et al. Cortical folding abnormalities in schizophrenia patients with resistant auditory hallucinations. Neuroimage. 2008;39(3):927-35.

23. Highley JR, DeLisi LE, Roberts N, Webb JA, Relja M, Razi K, et al. Sex-dependent effects of schizophrenia: an MRI study of gyral folding, and cortical and white matter volume. Psychiatry Res. 2003;124(1):11-23.

24. Vogeley K, Schneider-Axmann T, Pfeiffer U, Tepest R, Bayer TA, Bogerts B, et al. Disturbed gyrification of the prefrontal region in male schizophrenic patients: A morphometric postmortem study. Am J Psychiatry. 2000;157(1):34-9.

25. Highley JR, DeLisi LE, Roberts N, Webb JA, Relja M, Razi K, et al. Sex-dependent effects of schizophrenia: an MRI study of gyral folding, and cortical and white matter volume. Psychiatry research. 2003;124(1):11-23.

26. Palaniyappan L, Liddle PF. Aberrant cortical gyrification in schizophrenia: a surface-based morphometry study. J Psychiatry Neurosci. 2012;37(6):399-406.

27. Narr KL, Bilder RM, Toga AW, Woods RP, Rex DE, Szeszko PR, et al. Mapping cortical thickness and gray matter concentration in first episode schizophrenia. Cereb Cortex. 2005;15(6):708-19.

28. Narr KL, Toga AW, Szeszko P, Thompson PM, Woods RP, Robinson D, et al. Cortical thinning in cingulate and occipital cortices in first episode schizophrenia. Biol Psychiatry. 2005;58(1):32-40.

29. Lewine RR, Hudgins P, Brown F, Caudle J, Risch SC. Differences in qualitative brain morphology findings in schizophrenia, major depression, bipolar disorder, and normal volunteers. Schizophr Res. 1995;15(3):253-9.

30. Bullmore E, Brammer M, Harvey I, Murray R, Ron M. Cerebral hemispheric asymmetry revisited: effects of handedness, gender and schizophrenia measured by radius of gyration in magnetic resonance images. Psychol Med. 1995;25(2):349-63.

31. Flaum M, Arndt S, Andreasen NC. The role of gender in studies of ventricle enlargement in schizophrenia: a predominantly male effect. Am J Psychiatry. 1990;147(10):1327-32.

32. Frazier JA, Hodge SM, Breeze JL, Giuliano AJ, Terry JE, Moore CM, et al. Diagnostic and sex effects on limbic volumes in early-onset bipolar disorder and schizophrenia. Schizophr Bull. 2008;34(1):37-46.

33. APA. Diagnostic and Statistical Manual of Mental Disorders, DSM-IV. 4th ed. Washington, DC.: American Psychiatric Press; 1994.

34. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. 1971;9(1):97-113.

35. Canada EI. *National Occupational Classification (NOC): Occupational descriptions*. Ottawa: Canada Communication Group Publishing *(Human Resources Development Canada)*; 1993.

36. Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry. 2003;64(6):663-7.

37. First M, Spitzer, RL., Gibbon, M., & Williams, JBW. Structured Clinical Interview for DSM-IV Axis I Disorders-Non-Patient Edition (SCID-I/NP, Version 2.0-8/98 revision). NewYork: Biometrics Research Department, NewYork State Psychiatric Institute; 1998.

38. Kay SR, Opler, L.A., Fiszbein. A. Positive and Negative Syndrome Scale (PANSS) Rating Manual

Multihealth Systems I, editor. Toronto, Canada1992.

39. Lyttelton O, Boucher M, Robbins S, Evans A. An unbiased iterative group registration template for cortical surface analysis. Neuroimage. 2007;34(4):1535-44.

40. Zijdenbos AP, Forghani R, Evans AC. Automatic "pipeline" analysis of 3-D MRI data for clinical trials: application to multiple sclerosis. IEEE Trans Med Imaging. 2002;21(10):1280-91.

41. Sled JG, Pike GB. Standing-wave and RF penetration artifacts caused by elliptic geometry: an electrodynamic analysis of MRI. IEEE Trans Med Imaging. 1998;17(4):653-62.

42. Collins D, Evans AC. ANIMAL: Validation and Applications of Non-Linear Registration-Based Segmentation

International Journal of Pattern Recognition and Artificial Intelligence. 1997;11:1271-94.

43. Robbins S, Evans AC, Collins DL, Whitesides S. Tuning and comparing spatial normalization methods. Med Image Anal. 2004;8(3):311-23.

44. Collins DL, Neelin P, Peters TM, Evans AC. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. J Comput Assist Tomogr. 1994;18(2):192-205.

45. Van Essen DC, Dierker D, Snyder AZ, Raichle ME, Reiss AL, Korenberg J. Symmetry of cortical folding abnormalities in Williams syndrome revealed by surface-based analyses. J Neurosci. 2006;26(20):5470-83.

46. Lotjonen J, Reissman PJ, Magnin IE, Nenonen J, Katila T. A triangulation method of an arbitrary point set for biomagnetic problems. IEEE Trans Magn. 1998;34:2228-33.

47. Im K, Lee JM, Lyttelton O, Kim SH, Evans AC, Kim SI. Brain size and cortical structure in the adult human brain. Cereb Cortex. 2008;18(9):2181-91.

48. Van Essen DC, Drury HA. Structural and functional analyses of human cerebral cortex using a surface-based atlas. J Neurosci. 1997;17(18):7079-102.

49. Chung MK, Worsley KJ, Robbins S, Paus T, Taylor J, Giedd JN, et al. Deformation-based surface morphometry applied to gray matter deformation. Neuroimage. 2003;18(2):198-213.

50. Chung MK, Robbins SM, Dalton KM, Davidson RJ, Alexander AL, Evans AC. Cortical thickness analysis in autism with heat kernel smoothing. Neuroimage. 2005;25(4):1256-65.

51. Lerch JP, Evans AC. Cortical thickness analysis examined through power analysis and a population simulation. Neuroimage. 2005;24(1):163-73.

52. Diggle PJ, Liang KY, Zeger SL. Analysis of Longitudinal Data. . Oxford: Oxford University Press; 1994.

53. Genovese CR, Lazar NA, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage. 2002;15(4):870-8.

54. Nesvag R, Schaer M, Haukvik UK, Westlye LT, Rimol LM, Lange EH, et al. Reduced brain cortical folding in schizophrenia revealed in two independent samples. Schizophr Res. 2014;152(2-3):333-8.

55. Schultz CC, Koch K, Wagner G, Roebel M, Nenadic I, Schachtzabel C, et al. Complex pattern of cortical thinning in schizophrenia: results from an automated surface based analysis of cortical thickness. Psychiatry research. 2010;182(2):134-40.

56. Arango C, Kahn R. Progressive brain changes in schizophrenia. Schizophr Bull. 2008;34(2):310-1.

57. Cahn W, Hulshoff Pol HE, Bongers M, Schnack HG, Mandl RC, Van Haren NE, et al. Brain morphology in antipsychotic-naive schizophrenia: a study of multiple brain structures. Br J Psychiatry Suppl. 2002;43:s66-72.

58. Cahn W, Hulshoff Pol HE, Lems EB, van Haren NE, Schnack HG, van der Linden JA, et al. Brain volume changes in first-episode schizophrenia: a 1-year follow-up study. Arch Gen Psychiatry. 2002;59(11):1002-10.

59. DeLisi LE, Sakuma M, Tew W, Kushner M, Hoff AL, Grimson R. Schizophrenia as a chronic active brain process: a study of progressive brain structural change subsequent to the onset of schizophrenia. Psychiatry Res. 1997;74(3):129-40.

60. DeLisi LE, Tew W, Xie S, Hoff AL, Sakuma M, Kushner M, et al. A prospective follow-up study of brain morphology and cognition in first-episode schizophrenic patients: preliminary findings. Biol Psychiatry. 1995;38(6):349-60.

61. Lieberman J, Chakos M, Wu H, Alvir J, Hoffman E, Robinson D, et al. Longitudinal study of brain morphology in first episode schizophrenia. Biol Psychiatry. 2001;49(6):487-99.

62. Wood SJ, Pantelis C, Velakoulis D, Yucel M, Fornito A, McGorry PD. Progressive changes in the development toward schizophrenia: studies in subjects at increased symptomatic risk. Schizophr Bull. 2008;34(2):322-9.

63. Brans RG, van Haren NE, van Baal GC, Staal WG, Schnack HG, Kahn RS, et al. Longitudinal MRI study in schizophrenia patients and their healthy siblings. Br J Psychiatry. 2008;193(5):422-3.

64. Cahn W, Rais M, Stigter FP, van Haren NE, Caspers E, Hulshoff Pol HE, et al. Psychosis and brain volume changes during the first five years of schizophrenia. Eur Neuropsychopharmacol. 2009;19(2):147-51.

65. Hulshoff Pol HE, Kahn RS. What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. Schizophr Bull. 2008;34(2):354-66.

66. Guerguerian R, Lewine RR. Brain torque and sex differences in schizophrenia. Schizophr Res. 1998;30(2):175-81.

67. Narr K, Thompson P, Sharma T, Moussai J, Zoumalan C, Rayman J, et al. Three-dimensional mapping of gyral shape and cortical surface asymmetries in schizophrenia: gender effects. Am J Psychiatry. 2001;158(2):244-55.

68. van Haren NE, Hulshoff Pol HE, Schnack HG, Cahn W, Brans R, Carati I, et al. Progressive brain volume loss in schizophrenia over the course of the illness: evidence of maturational abnormalities in early adulthood. Biol Psychiatry. 2008;63(1):106-13.

69. Wood SJ, Velakoulis D, Smith DJ, Bond D, Stuart GW, McGorry PD, et al. A longitudinal study of hippocampal volume in first episode psychosis and chronic schizophrenia. Schizophr Res. 2001;52(1-2):37-46.

70. van Haren NE, Hulshoff Pol HE, Schnack HG, Cahn W, Mandl RC, Collins DL, et al. Focal gray matter changes in schizophrenia across the course of the illness: a 5-year follow-up study. Neuropsychopharmacology. 2007;32(10):2057-66.

71. DeLisi LE, Sakuma M, Maurizio AM, Relja M, Hoff AL. Cerebral ventricular change over the first 10 years after the onset of schizophrenia. Psychiatry Res. 2004;130(1):57-70.

72. Hu HH, Guo WY, Chen HY, Wang PS, Hung CI, Hsieh JC, et al. Morphological regionalization using fetal magnetic resonance images of normal developing brains. Eur J Neurosci. 2009;29(8):1560-7.

73. Onitsuka T, McCarley RW, Kuroki N, Dickey CC, Kubicki M, Demeo SS, et al. Occipital lobe gray matter volume in male patients with chronic schizophrenia: A quantitative MRI study. Schizophr Res. 2007;92(1-3):197-206.

74. Bijanki KR, Hodis B, Magnotta VA, Zeien E, Andreasen NC. Effects of age on white matter integrity and negative symptoms in schizophrenia. Schizophr Res. 2015;161(1):29-35.

75. Mitelman SA, Shihabuddin L, Brickman AM, Hazlett EA, Buchsbaum MS. MRI assessment of gray and white matter distribution in Brodmann's areas of the cortex in patients with schizophrenia with good and poor outcomes. The American journal of psychiatry. 2003;160(12):2154-68.

76. Mazhari S, Moghadas Tabrizi Y. Abnormalities of mental rotation of hands associated with speed of information processing and executive function in chronic schizophrenic patients. Psychiatry Clin Neurosci. 2014;68(6):410-7.

77. Wang Q, Cheung C, Deng W, Li M, Huang C, Ma X, et al. Fronto-parietal white matter microstructural deficits are linked to performance IQ in a first-episode schizophrenia Han Chinese sample. Psychol Med. 2013;43(10):2047-56.

78. Tagamets MA, Cortes CR, Griego JA, Elvevag B. Neural correlates of the relationship between discourse coherence and sensory monitoring in schizophrenia. Cortex. 2014;55:77-87.

79. Yun JY, Hur JW, Jung WH, Jang JH, Youn T, Kang DH, et al. Dysfunctional role of parietal lobe during self-face recognition in schizophrenia. Schizophr Res. 2014;152(1):81-8.

80. Jou RJ, Hardan AY, Keshavan MS. Reduced cortical folding in individuals at high risk for schizophrenia: a pilot study. Schizophr Res. 2005;75(2-3):309-13.

81. Luders E, Thompson PM, Narr KL, Toga AW, Jancke L, Gaser C. A curvature-based approach to estimate local gyrification on the cortical surface. Neuroimage. 2006;29(4):1224-30.

82. Crow TJ. The 'big bang' theory of the origin of psychosis and the faculty of language. Schizophr Res. 2008;102(1-3):31-52.

83. DeLisi LE, Hoff AL, Neale C, Kushner M. Asymmetries in the superior temporal lobe in male and female first-episode schizophrenic patients: measures of the planum temporale and superior temporal gyrus by MRI. Schizophr Res. 1994;12(1):19-28.

84. Pruessner M, Boekestyn L, Bechard-Evans L, Abadi S, Vracotas N, Joober R, et al. Sex differences in the cortisol response to awakening in recent onset psychosis. Psychoneuroendocrinology. 2008;33(8):1151-4.

85. Jansen LM, Gispen-de Wied CC, Gademan PJ, De Jonge RC, van der Linden JA, Kahn RS. Blunted cortisol response to a psychosocial stressor in schizophrenia. Schizophr Res. 1998;33(1-2):87-94.

86. Andreasen NC, Flashman L, Flaum M, Arndt S, Swayze V, 2nd, O'Leary DS, et al. Regional brain abnormalities in schizophrenia measured with magnetic resonance imaging. JAMA. 1994;272(22):1763-9.

87. Bogerts B, Ashtari M, Degreef G, Alvir JM, Bilder RM, Lieberman JA. Reduced temporal limbic structure volumes on magnetic resonance images in first episode schizophrenia. Psychiatry Res. 1990;35(1):1-13.

88. Rao ML, Kolsch H. Effects of estrogen on brain development and neuroprotection--implications for negative symptoms in schizophrenia. Psychoneuroendocrinology. 2003;28 Suppl 2:83-96.

89. Hafner H. Gender differences in schizophrenia. Psychoneuroendocrinology. 2003;28 Suppl 2:17-54.

90. Castle DJ, Abel K, Takei N, Murray RM. Gender differences in schizophrenia: hormonal effect or subtypes? Schizophr Bull. 1995;21(1):1-12.

91. Riecher-Rossler A, Hafner H, Dutsch-Strobel A, Oster M, Stumbaum M, van Gulick-Bailer M, et al. Further evidence for a specific role of estradiol in schizophrenia? Biol Psychiatry. 1994;36(7):492-4.

92. Riecher-Rossler A, Hafner H, Stumbaum M, Maurer K, Schmidt R. Can estradiol modulate schizophrenic symptomatology? Schizophr Bull. 1994;20(1):203-14.

93. Jones EG. Cortical development and thalamic pathology in schizophrenia. Schizophr Bull. 1997;23(3):483-501.

94. Andreasen NC, Paradiso S, O'Leary DS. "Cognitive dysmetria" as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? Schizophr Bull. 1998;24(2):203-18.

95. Clinton SM, Meador-Woodruff JH. Thalamic dysfunction in schizophrenia: neurochemical, neuropathological, and in vivo imaging abnormalities. Schizophr Res. 2004;69(2-3):237-53.

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Figure legends:

Figure 1a and 1b: Figures show more rapid decrease in GI bilaterally with progressive age in the patient group compared to controls. (a) Represents Group-by-Age interaction in the right hemisphere regression GI (r^2=.121; β=-.347; t=-3.592; p=.001, df=94). (b) Represents group-by-Age interaction in the left hemisphere GI (r^2=.104; β=-.323; t=-3.311; p=.001, df=94)

Figure 2a and 2b: Figures show more showing that males with schizophrenia had greater GI reductions bilaterally yet more pronounced in the right hemisphere with progressive age compared to females with schizophrenia (a) represents Age x Sex interaction on the right hemisphere GI (r^2=.212; β=-.461; t=-3.523; p=.001, df=94). (b) Represents Age x Sex interaction in the left hemisphere GI (r^2=.121; β=-.348; t=-2.514; p=.016, df=94)

Figure 3:. Represents interaction between duration of illness and sex (r^2=.244; β=-.494; t=-3.856; p=.0001, df=46), demonstrating greater decrease in GI in the right hemisphere with the duration of illness only in males with schizophrenia.

Figure 4: Represent higher GI in Female controls in comparison to Male controls and both groups of patients.

Figure 5: Represents variation in GI, top image shows low gyrification index and bottom image show high gyrification index.

Table 1. Clinical assessments in schizophrenia patients

	SZ-M	Range	SZ-F	Range	P value (df=46)
	Mean (SD)		Mean (SD)		
Age (years)	31.25 (7.96)	20-49	33.04 (8.38)	21-51	0.452
Duration of illness (years)	11.04 (10.63)	2-25	8.04 (7.55)	1-27	0.265
Age of onset (years)	21.47 (4.78)	14-35	25.83 (7.37)	18-48	0.021
PANSS positive score	17.083 (5.76)	8-29	19.62 (7.49)	9-34	0.194
PANSS negative score	16.12 (4.45)	10-26	20.79 (7.69)	9-39	0.038**
PANSS general score	36.96 (7.11)	25-54	42.41 (12.66)	24-72	0.072
PANSS total score	70.92 (13.92)	46-107	82.83 (26.08)	41-140	0.05**
Chlorpromazine equivalence (mg/day)	542.29 (372.09)	100-1500	438.71 (276.35)	66-1100	0.279

Table 2. Lobar GI measures

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

Figure 1a. Representing Group x Age interaction in the right hemisphere

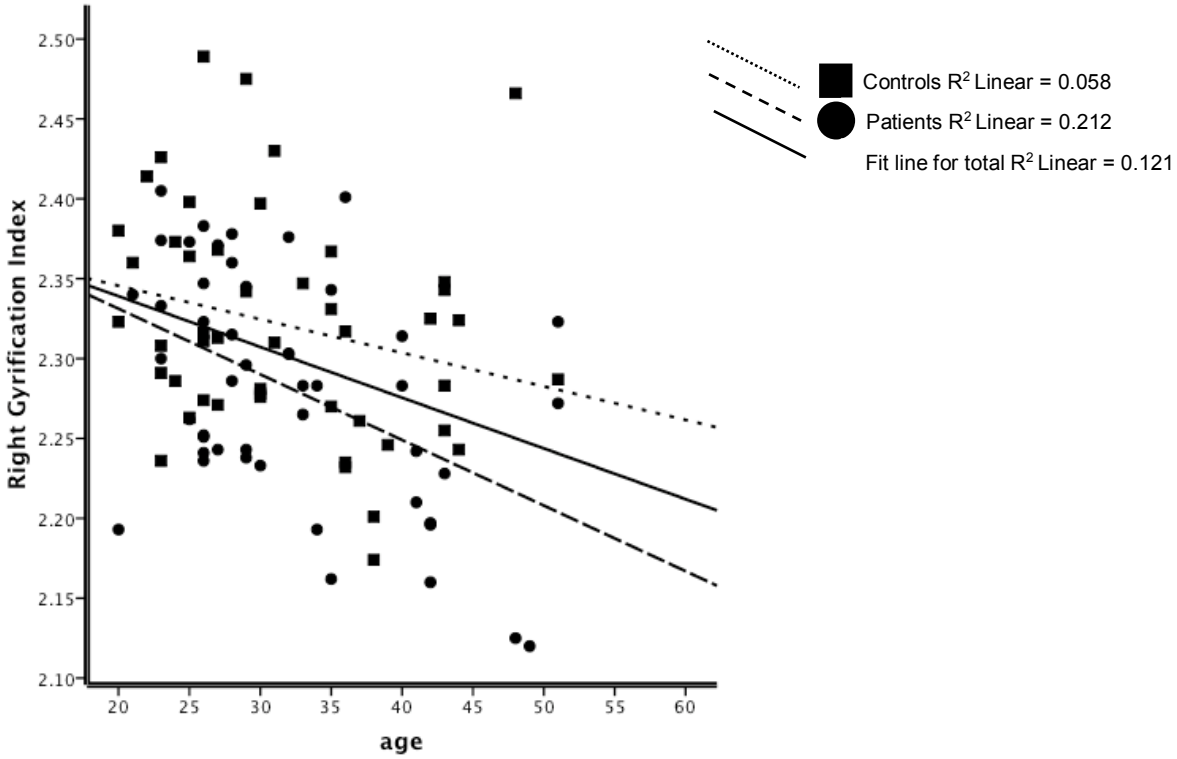


Figure 1b. Representing Group x Age interaction in the left hemisphere

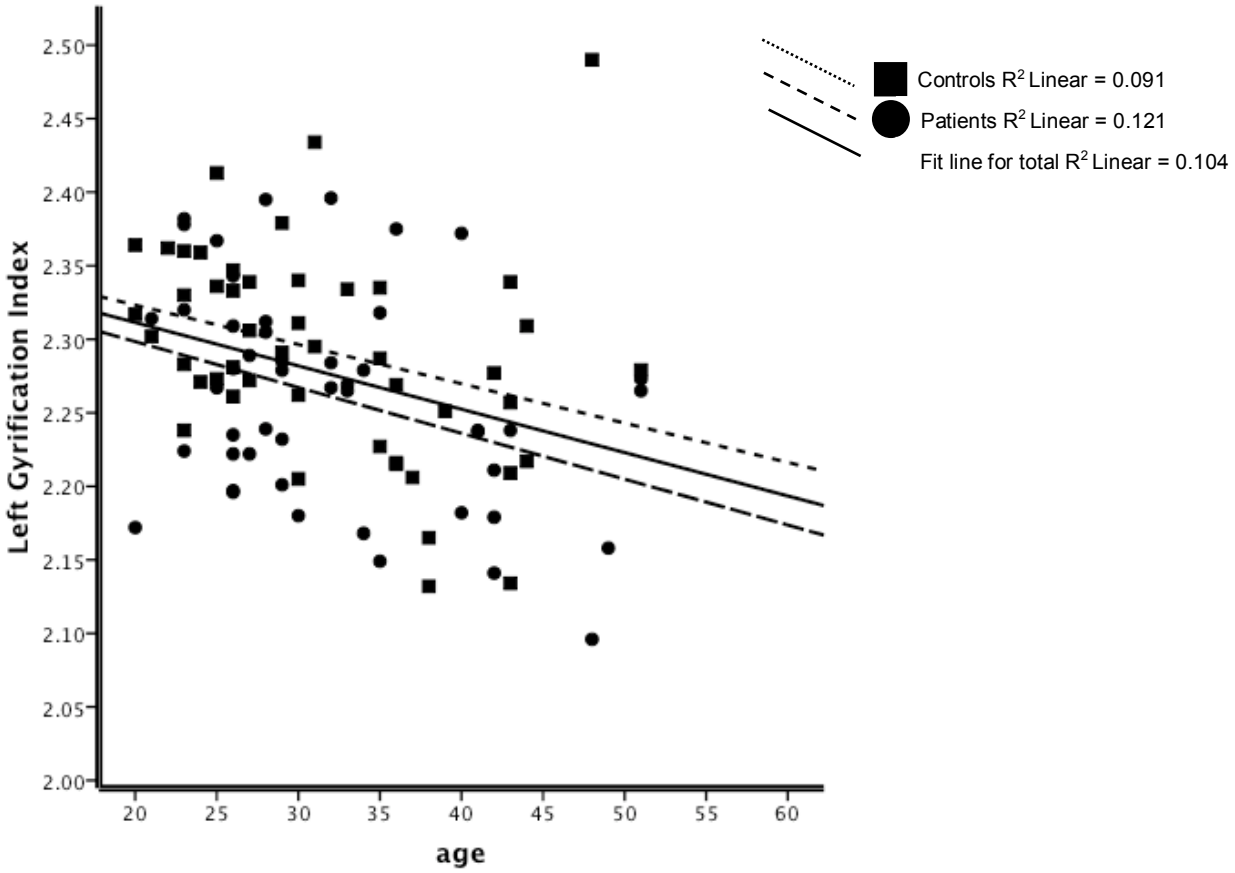


Figure 2a. Representing Age x Sex interaction on the right hemisphere

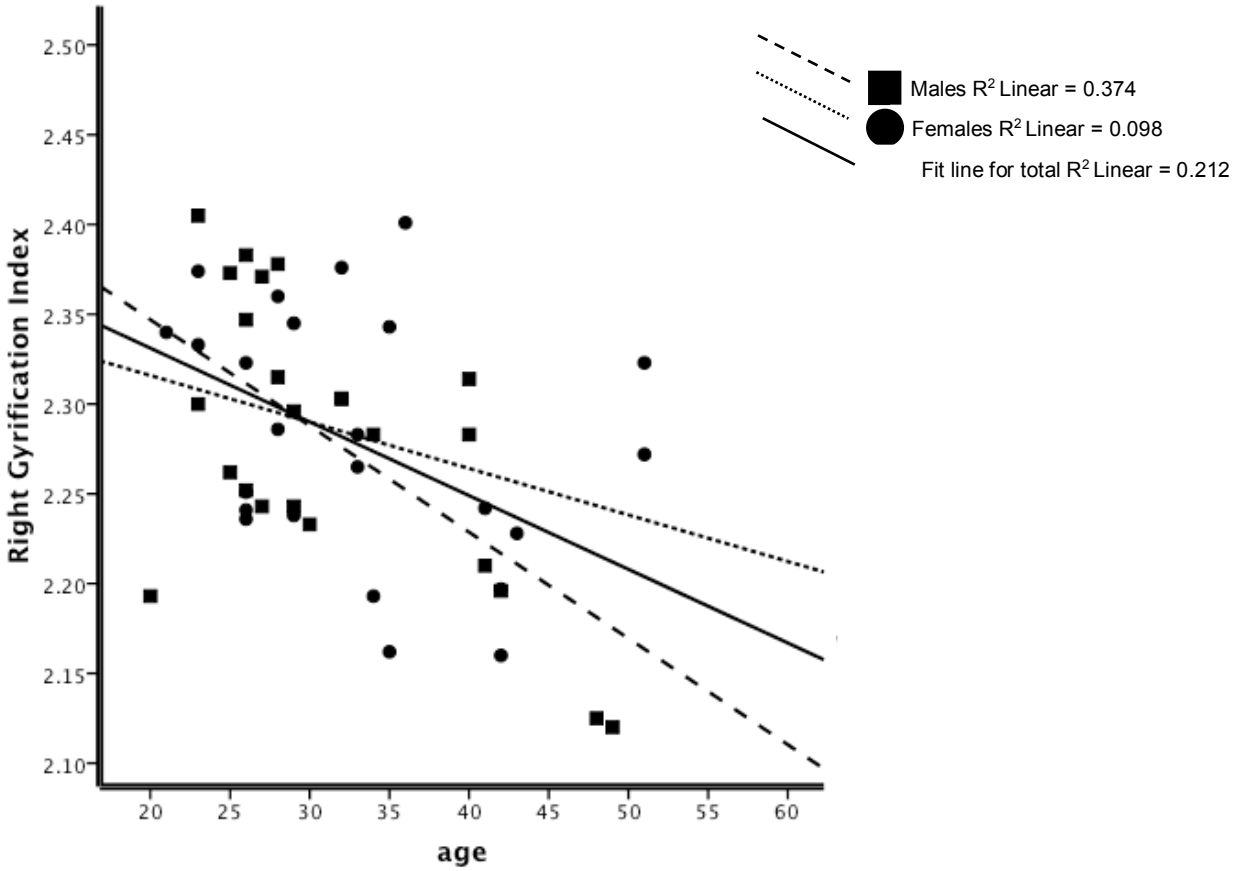


Figure 2b. Representing Age x Sex interaction on the left hemisphere

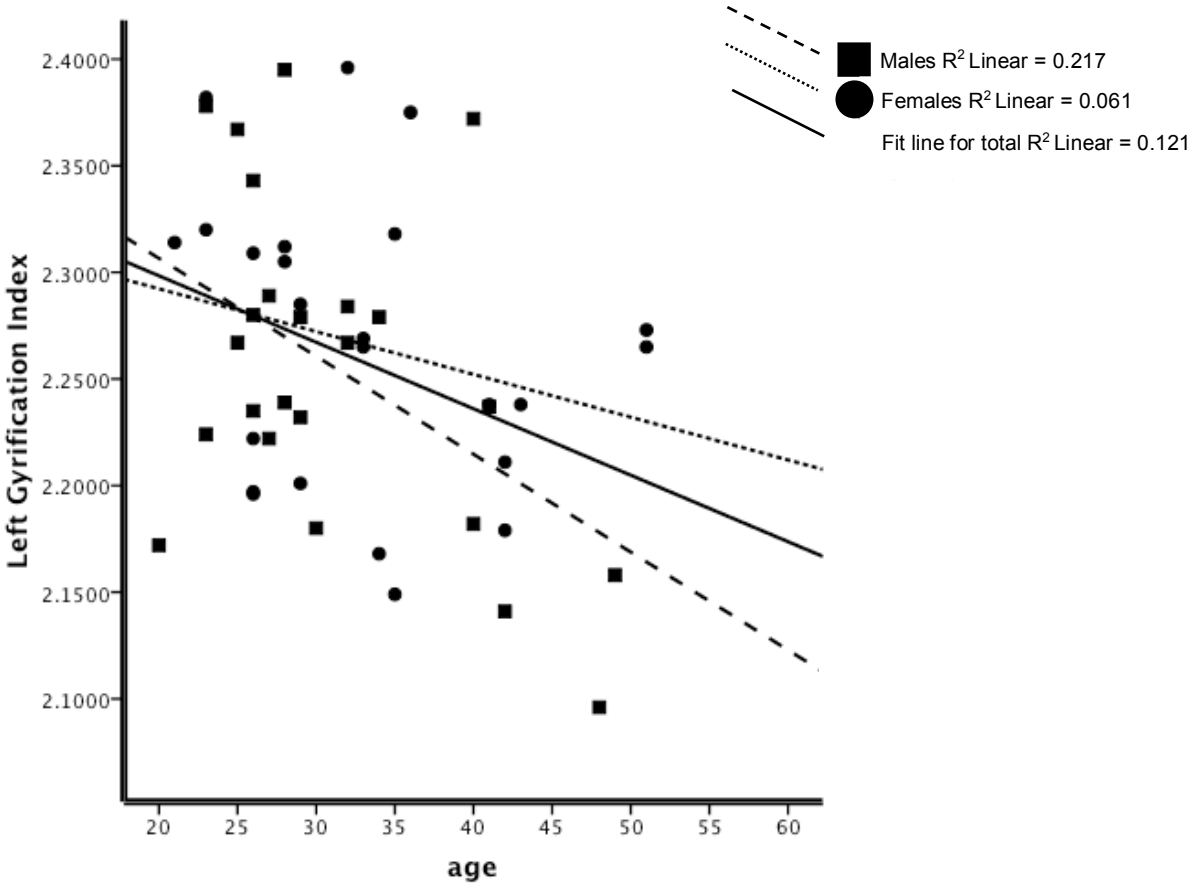


Figure 3. Duration of illness and Sex interaction in right hemisphere

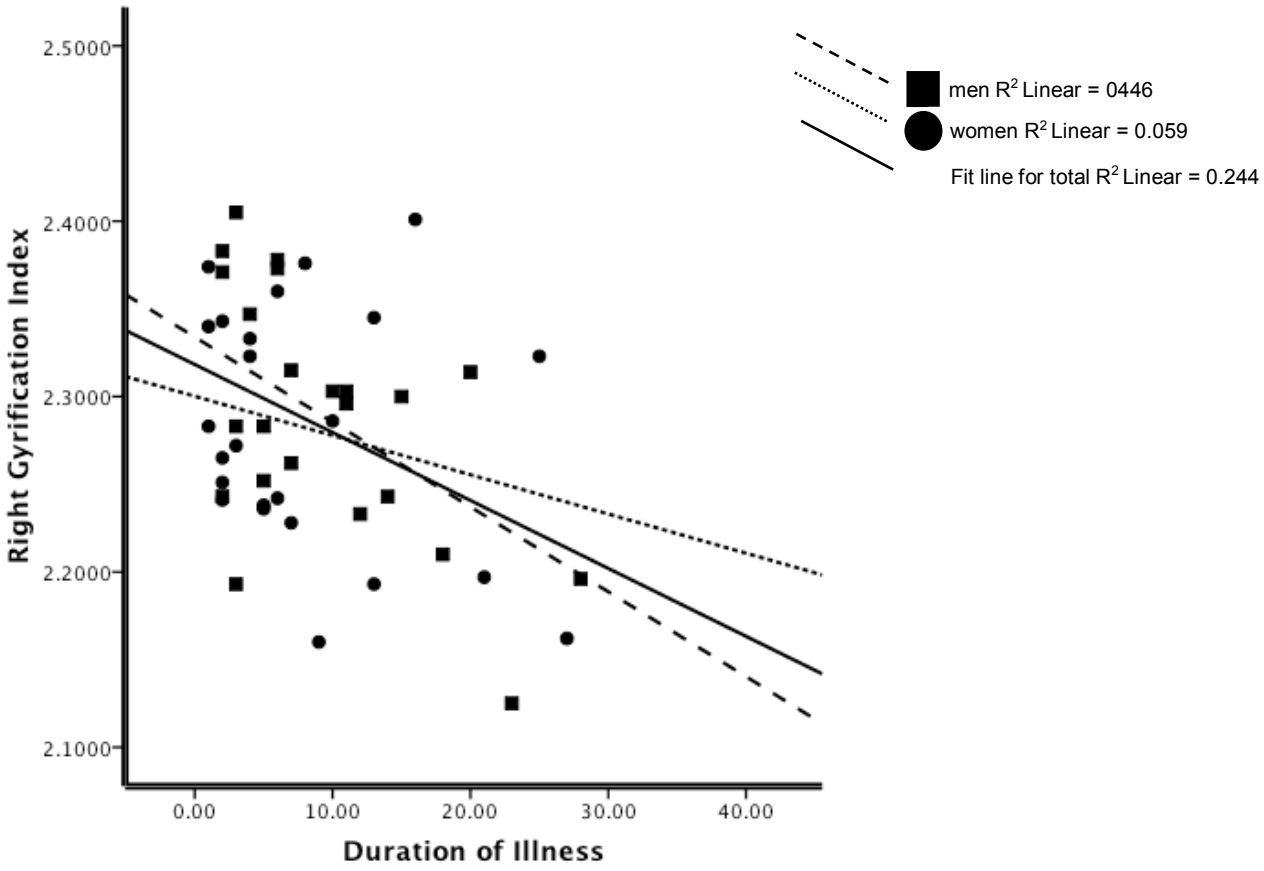
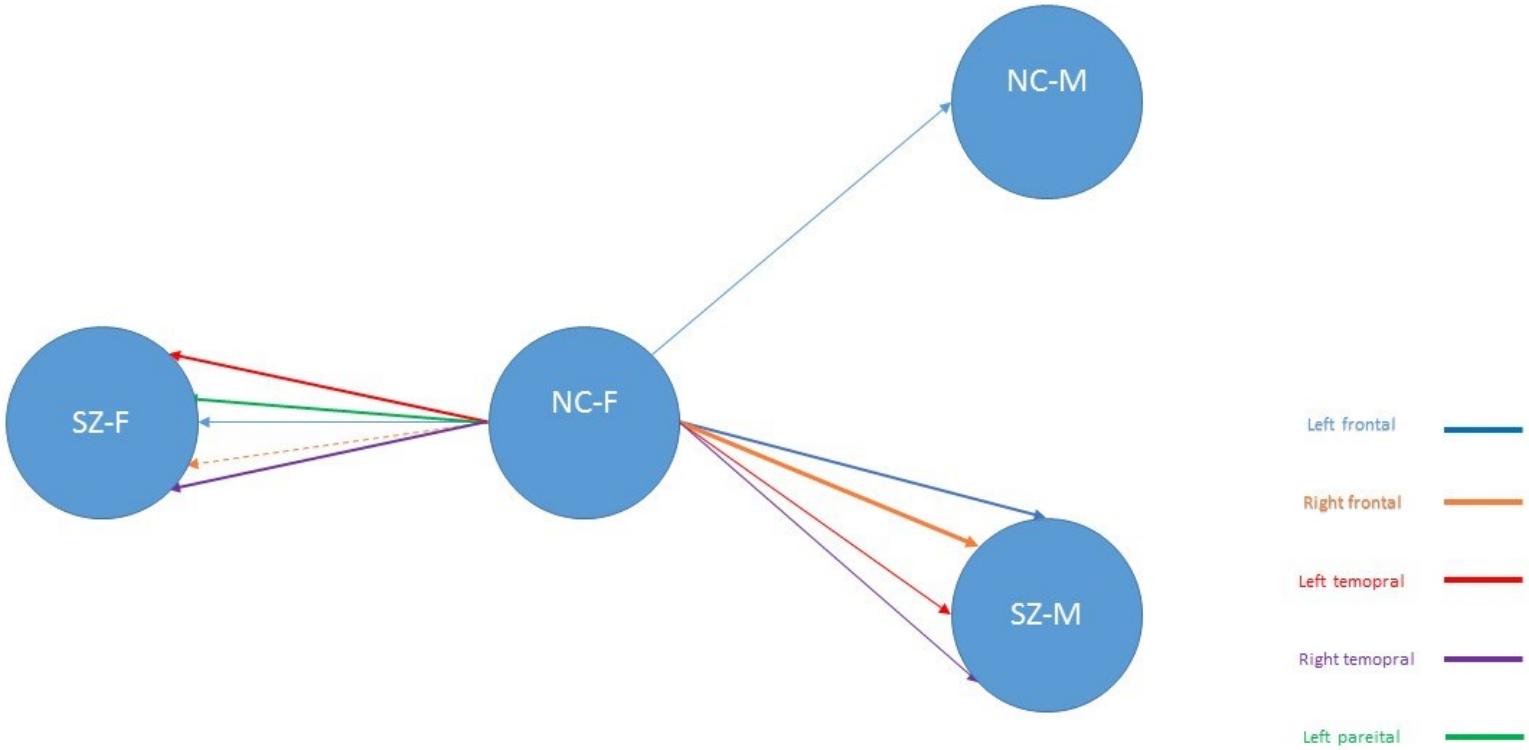
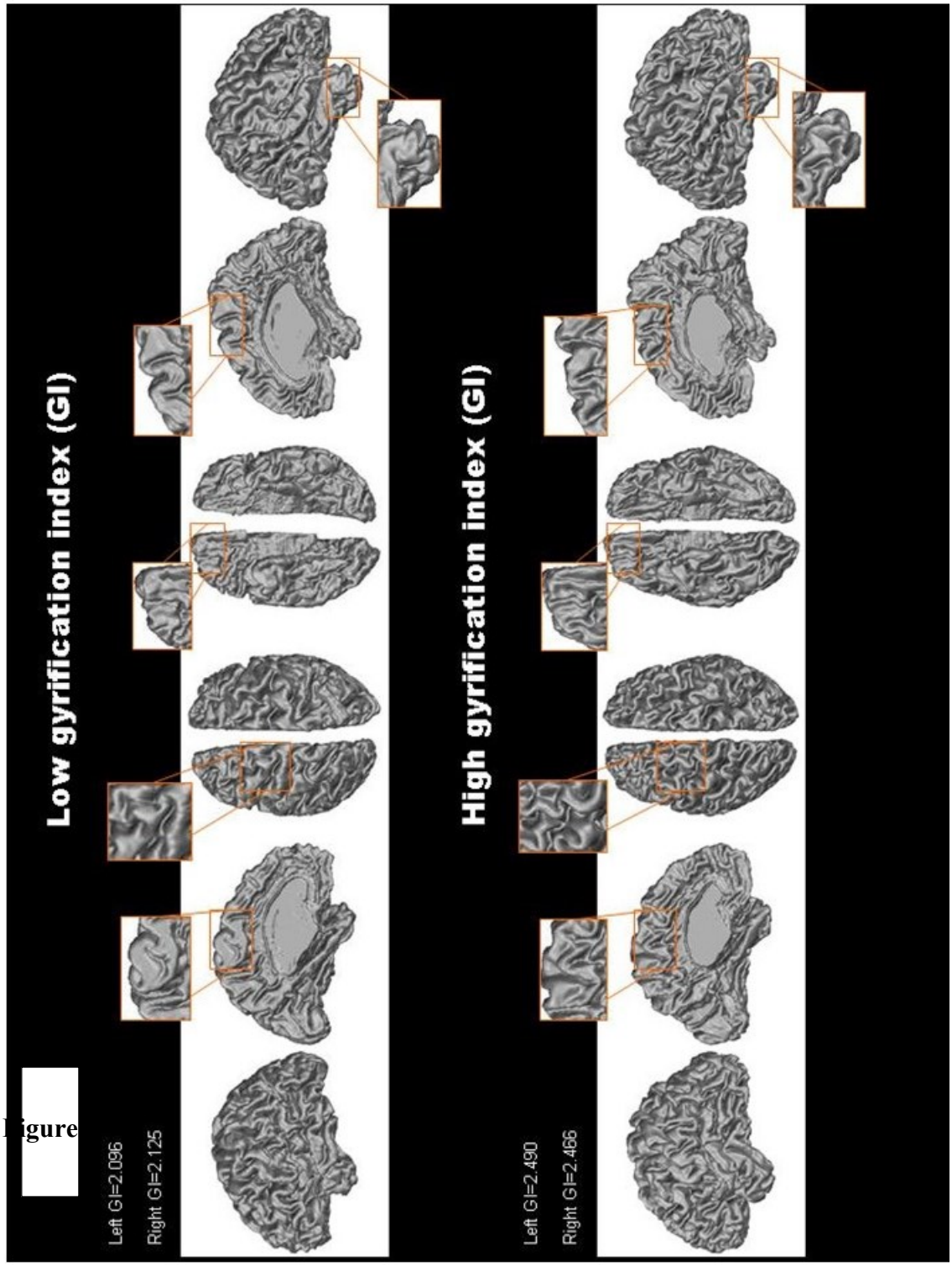


Figure 4. Gyrification index increases in female controls in comparison to male controls and both groups of patients.




Low gyrification index (GI)
Left GI=2.096
Right GI=2.125
High gyrification index (GI)
Left GI=2.490
Right GI=2.466

Figure

6 Article 2

The following work has been re-submitted to *Psychiatry Research Journal* after including the reviewer' corrections under the title: *"Symptom based gray and white matter densities in schizophrenia"*. We are awaiting the journal's reply.

In the first study, an important and unanticipated finding was the fact that symptoms correlated only with the GI of the occipital lobe, while, abnormalities in GI in our group of schizophrenia patients in comparison to normal controls were found in several cerebral regions. This intriguing finding lead to the work presented in the second paper, were we postulated that deeper structures and white matter are associated with symptoms of schizophrenia, and that this relation differs in male and female patients. Using voxel based morphometry, association between greater WMD and more severe symptom scores of conceptual disorganization and attention deficits were revealed. However, when considering the two sexes individually it became clear that there were no specific correlations between total GM, WM, CSF, or total brain densities and schizophrenia symptoms in female patients, while WMD in males correlated negatively with ideas of grandiosity, and positively with conceptual disorientation and attention deficits. To our knowledge, this is the first report of a direct relationship between white matter density and conceptual disorganization and attention deficits in schizophrenia and the first report of sex differences in correlation between symptoms and white matter densities.

Article 2

Symptom based gray and white matter densities in schizophrenia

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Abstract

We investigated the association between gray matter density (GMD) and white matter density (WMD) phenotypes and positive and negative symptoms in 40 schizophrenia patients (SZ). Additionally, cerebral volumes 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. In addition, WMD reduction was found in the inferior frontal and posterior parietal regions in SZ relative to NC. GMD in the insula/caudate correlated with positive symptoms, while GMD in the middle frontal gyrus and cerebellum (uvula) correlated with negative symptoms. WMD in the middle frontal and superior frontal regions correlated with positive and negative symptoms respectively. Invers correlations were found between GMD in the parietal lobe and the uvula with positive symptoms. Additionally, an inverse correlation was found between GMD in the cerebellum (anterior lobe) and negative symptoms. Inverse correlation was also found in the WMD of the occipital region and superior frontal regions with positive and negative symptoms respectively. Comparison between male groups revealed decreased total GMD in SZ-M, while no differences were observed between female groups. Fronto-temporal reductions in patients support previous studies. These correlational findings suggest that symptom profiles in schizophrenia show unique GM/WM phenotypes. Our results reject the notion that all patients might share a core network of neuropathology.

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

Introduction

Schizophrenia is thought to be underpinned by neurodevelopmental abnormalities of brain gray matter and white matter function, structure and connectivity (1-4). 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 (i.e., hallucinations, delusions, and paranoid ideation), and negative symptoms (i.e., poverty of thought and loss of motivation) (5-7). 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.

Functional and structural alterations in cerebral gray matter (GM) and white matter (WM) in schizophrenia, particularly in 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 are well established (8-13). 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 negative symptoms have greater impact on global functioning than positive symptoms because of their undetermined etiology and resistance to treatment (14). Grouping patients by specific genetic, neuroanatomical and symptoms endophenotypes (15, 16) may yield more specific findings.

Sex differences have an important impact on symptoms in schizophrenia. 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 (17-26). 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 (27). Neurostructural differences in males and females with schizophrenia have also been reported. Imaging studies on sex–dependent brain abnormalities have consistently reported more severe disturbance in males than in females with schizophrenia: reduced prefrontal volumes, reduced anterior temporal horn and medial temporal lobe volumes, more specifically amygdala, hippocampus, superior temporal and larger ventricular-brain ratios (VBR)(28-37). 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 (38). 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, overall more sever cortical abnormalities were observed in male patients. An important and unanticipated finding was 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 found 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. We hypothesized that deeper 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.

Methods

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 (39) 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) (40) 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, no significant differences were found 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. Affective, schizoaffective, and schizophreniform psychoses were excluded. Control participants were screened with the non-patients edition of the Clinical Interview for DSM-III (SCID) (41). The positive and negative syndrome scale (PANSS) was used to rate symptom severity (5, 7). 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) (42).

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

---------Insert table 1 around here-------

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.

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 the latest version of 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 the latest version of 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 (43). 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 white matter (WM) maps were then modulated with the resulting Jacobian determinant maps and smoothed with an 8-mm FWHM Gaussian kernel.

Total GMD, WMD and 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) (43, 44) 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 (45). 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 (45). 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.

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. Separate regression analyses of total GMD and WMD were performed on the best linear unbiased predictors. To that end, we used the forward stepwise approach combined with the Akaike's Information Criterion Corrected (AICC) (46). 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., $p<0.05$).

Results

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 rectal and the left posterior parietal regions in comparison to NC (Table 2).

--------Insert table 2 and Figure 1 about here-------

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

Inversed significant correlations were found between positive symptoms and GMD both the right parietal (precuneus), and the posterior lobe of left cerebellum (uvula). Additionally, inversed correlations were found between negative symptoms and the anterior lobe of the left

cerebellum. Concerning WMD, positive correlations were found with positive symptoms in the right middle frontal region, while negative symptoms were positively correlated with WMD in the right superior frontal region. Negative correlations were found between positive symptoms, the right inferior occipital, and the right occipital cuneus. Negative symptoms correlated negatively with the left superior frontal (Table 4, 3).

--------Insert Table 3 and 4 and Figure 2 and 3 about here-------

Comparison between male groups revealed decreased total GMD (F=.126 t=2.217 df =40 p=.32) while no differences were observed in female groups. 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).

-------Insert Figure 4 around here------

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

-------Insert Figures 5 and 7 around here------

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)..

-------Insert Figure 6 and 8 around here------

Results of clinical assessments:

No differences were found between SZ-M and SZ-F when using the total PANSS scores of: negative, positive, or general items. When analyses were performed by individual item, no differences were found 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).

----------Insert Table 5 around here-------

Cognitive behavioral assessments:

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

--------Insert Table 6 around here-------

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. As hypothesized, males with schizophrenia showed lower GMD compared to same-

sex normal controls, while no difference were observed in female groups. Females with schizophrenia showed no correlations between brain densities and symptoms, while male patients showed several correlations, specifically between WMD and disorientation, and between both GMD and WMD and attention deficits. In addition, inverse correlation were observed between WMD and ideas of grandiosity. In addition to our findings on sex differences, 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 and the posterior lobe of right cerebellum (uvula). Inverse correlation were also observed between positive symptoms 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. Inverse correlation between positive symptoms and WMD were observed 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. Individual symptoms such as conceptual disorganization were also found to correlate with both GMD and WMD. Inverse correlations were observed between lack of spontaneity and hallucinations and GMD. Hostility and grandiosity inversely correlated with WMD.

The finding regarding group main effect differences between NC and SZ is consistent with the literature (47). The anterior cingulate finding is of particular interest since a recent study showed that “at risk” subjects who actually develop psychosis had significantly smaller anterior cingulate volumes (48). Furthermore, in a recent meta-analysis, Sepede and colleagues (2014) argued that alterations of the anterior cingulate cortex seemed to be more common in schizophrenia than in bipolar disorder (8). The increased GMD of the posterior cingulate in the schizophrenia group may indicate a compensatory mechanism in response to the anterior cingulate deficit.

We have also found decreased GMD in the left middle temporal, which represents one of the most consistent findings in patients with schizophrenia (49, 50).

Our significant finding of the positive relationship between PANSS positive symptoms and the insula and the caudate density is also consistent with some previous studies. The insula has been involved in emotional interoceptive representations (51) and positive symptoms were shown

to correlate with reward anticipation signal in the insula in individuals at high risk to develop psychosis (52). A recent study by Rolland et al., (2015) demonstrated that patients with acoustico-verbal hallucinations show bilaterally greater resting state functional connectivity in the insula (53). Similarly, Sepede and colleagues (2014) demonstrated that significantly altered functioning of the insula was found in schizophrenia, and proposed it as a candidate trait marker for psychosis (8). 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 (54-57). 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. A strong functional connectivity has been reported between the insula and caudate. The caudate have been reported be functionally connected with 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 (58-60). We should note however, that it might be related to medication (61).

The parietal cortex was negatively correlated with the PANSS positive symptoms. Conversely, the frontal cortex was positively correlated with the PANSS negative symptoms. 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. Subjects who developed schizophrenia had smaller volumes in the parietal cortex (48). The positive correlation in the middle frontal with negative symptoms is of particular interest. Several studies point out the importance of this region in emotion regulation (62-64), and in down-regulation of emotional processing (65) in normal population. A meta-analysis by Kohn et al. (2014) concludes that the middle frontal region (dorsolateral frontal cortex-DLPFC) plays a key role in action inhibition and proposes that it modulates “higher order ‘cold’ regulatory processes” (66). Of specific relevance to our results are findings by Smith et al., (2013) showing that a decrease in volume of the DLPFC is associated with improvement of depression symptoms in patients with depression (67). In view of these findings, it is reasonable to say that negative symptoms, which share several characteristics with major depression, are associated with over engagement of the DLPFC in affective inhibitory processes in schizophrenia patients.

Present findings point to the importance of the cerebellum in mediation of positive and negative symptoms and 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 (68). In 1995, Martin and Albers concluded that morphological and functional data support the role of the cerebellar dysfunction in the pathogenesis of schizophrenia (69). In their review, Andreasen & Pierson (2008) argued that the cerebellum plays a role in higher cognitive and emotional cortical functions (70). 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 (71). Based on our results, the cerebellum is mainly correlated with the PANSS negative symptoms. This may be in agreement with previous research findings asserting the cerebellum as an emotional pacemaker (72). 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 (72). 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 associated with deficits in several cognitive processes (73), perception and correction errors (72), source and self-monitoring (75), stimulus recognition (76), and reality monitoring (77, 78). The relation between these cognitive processes and the cerebellum are not fully understood.

Regarding WM abnormalities, we observed a strong relationship between the superior frontal region and negative symptoms. This finding is coherent with the fact that male patients showed an inverse correlation between WMD and ideas of grandiosity, and a positive correlation with conceptual disorientation and attention deficits. This is in agreement with previous studies concluding that abnormalities in the superior frontal executive region could explain negative symptoms (47, 79).

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 (the WAIS-III and Raven percentile tests) from the patients and normal group. Significant deficits were observed in the schizophrenia groups in all measures when compared to healthy subjects (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 (paper submitted), and several studies have shown abnormalities is these regions in relation with deficits in mental rotation abilities (80), IQ performance (81), language processing (82), and face recognition (83).

When examining sex-dependent differences, we noted that male patients had decreased total GMD when compared to normal control males, while no differences were observed in female groups. Several studies show that males with schizophrenia have more GM abnormalities than females with schizophrenia. Such abnormalities 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 females have more preserved cerebral morphology (28-37). Several authors have suggested that these differences are due to the neuroprotective effects of estrogen in females (84-86). In terms of correlation, females revealed no specific correlation between total GMD, WMD, CSF, or total brain volume and schizophrenia symptoms. In contrast, WMD in males inversely correlated with ideas of grandiosity, and positively with conceptual disorientation and attention deficits. To our knowledge, this is the first study to report a direct relation between white matter volume and these symptoms. Interestingly a study by Sallet et al., (2003) found correlations between cortical gyrification index and grandiosity (87). Gyrification index measures cortical folding, a feature that is hypothesized to represent underlying white matter (88). The white matter abnormalities are in support of neurodevelopmental disturbance that is more evident in males than females with schizophrenia.

Regardless of sex of patients, our exploratory prediction model of the linear regression relationship between GMD and WMD with the PANSS symptoms has produced stimulating results. The negative correlation between WMD and ideas of grandiosity remained significant after grouping male and female patients together. This in itself gives further support to the important role of sex differences in schizophrenia. Here we report for the first time the relation between 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 (89, 90).

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 (91), which are fundamental elements in the construction of conceptual disorganization. However, further studies are needed in schizophrenia to support this view.

In our study GMD was inversely correlated with hallucinations, in concordance with several studies showing a similar association with gray matter in the left superior temporal gyrus (92-94), left thalamus, left and right cerebellum (93) middle/inferior right prefrontal gyri (94), bilateral insula and left amygdala (92) (also see review by Aguilar et al., 2008) (95).

The intensity of lack of spontaneity and hallucination symptoms predicted the degree of GMD loss, while increased hostility and grandiosity symptoms predicted decreased WMD. Interestingly, the intensity of conceptual disorganization was a predicting factor of increased GMD and WMD in schizophrenia patients. To this end, future studies investigating the correlation between individual symptoms and specific cerebral regions are needed.

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) (42). 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.

Conclusion

Considerable heterogeneity remains across studies investigating changes in GM and WM volume 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. (96-99). 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.

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.

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. To this end, future studies should investigate the correlation between individual symptoms and specific cerebral regions.

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References

1. Andreasen NC. Understanding the causes of schizophrenia. The New England journal of medicine. 1999;340(8):645-7.
2. van Os J, Kapur S. Schizophrenia. Lancet. 2009;374(9690):635-45.
3. Insel TR. Rethinking schizophrenia. Nature. 2010;468(7321):187-93.
4. Jablensky A. The diagnostic concept of schizophrenia: its history, evolution, and future prospects. Dialogues Clin Neurosci. 2010;12(3):271-87.
5. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261-76.
6. Andreasen NC, Akiskal HS. The specificity of Bleulerian and Schneiderian symptoms: a critical reevaluation. The Psychiatric clinics of North America. 1983;6(1):41-54.
7. Kay SR, Opler LA, Lindenmayer JP. Reliability and validity of the positive and negative syndrome scale for schizophrenics. Psychiatry research. 1988;23(1):99-110.
8. Sepede G, Spano MC, Lorusso M, De Berardis D, Salerno RM, Di Giannantonio M, et al. Sustained attention in psychosis: Neuroimaging findings. World journal of radiology. 2014;6(6):261-73.
9. Wolf RC, Hose A, Frasch K, Walter H, Vasic N. Volumetric abnormalities associated with cognitive deficits in patients with schizophrenia. Eur Psychiatry. 2008;23(8):541-8.
10. Yamada M, Hirao K, Namiki C, Hanakawa T, Fukuyama H, Hayashi T, et al. Social cognition and frontal lobe pathology in schizophrenia: a voxel-based morphometric study. Neuroimage. 2007;35(1):292-8.
11. Honea R, Crow TJ, Passingham D, Mackay CE. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. The American journal of psychiatry. 2005;162(12):2233-45.
12. Bora E, Fornito A, Radua J, Walterfang M, Seal M, Wood SJ, et al. Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis. Schizophr Res. 2011;127(1-3):46-57.
13. Lui S, Deng W, Huang X, Jiang L, Ma X, Chen H, et al. Association of cerebral deficits with clinical symptoms in antipsychotic-naive first-episode schizophrenia: an optimized voxel-

based morphometry and resting state functional connectivity study. The American journal of psychiatry. 2009;166(2):196-205.

14. Kring AM, Gur RE, Blanchard JJ, Horan WP, Reise SP. The Clinical Assessment Interview for Negative Symptoms (CAINS): final development and validation. The American journal of psychiatry. 2013;170(2):165-72.

15. Jablensky A. Subtyping schizophrenia: implications for genetic research. Molecular psychiatry. 2006;11(9):815-36.

16. Glahn DC, Thompson PM, Blangero J. Neuroimaging endophenotypes: strategies for finding genes influencing brain structure and function. Human brain mapping. 2007;28(6):488-501.

17. Chang WC, Hui CL, Tang JY, Wong GH, Lam MM, Chan SK, et al. Persistent negative symptoms in first-episode schizophrenia: a prospective three-year follow-up study. Schizophr Res. 2011;133(1-3):22-8.

18. Fenton WS, McGlashan TH. Natural history of schizophrenia subtypes. II. Positive and negative symptoms and long-term course. Arch Gen Psychiatry. 1991;48(11):978-86.

19. Andreasen NC, Flaum M, Swayze VW, 2nd, Tyrrell G, Arndt S. Positive and negative symptoms in schizophrenia. A critical reappraisal. Arch Gen Psychiatry. 1990;47(7):615-21.

20. Ring N, Tantam D, Montague L, Newby D, Black D, Morris J. Gender differences in the incidence of definite schizophrenia and atypical psychosis--focus on negative symptoms of schizophrenia. Acta Psychiatr Scand. 1991;84(6):489-96.

21. Kay SR, Opler LA, Fiszbein A. Significance of positive and negative syndromes in chronic schizophrenia. Br J Psychiatry. 1986;149:439-48.

22. Schultz SK, Miller DD, Oliver SE, Arndt S, Flaum M, Andreasen NC. The life course of schizophrenia: age and symptom dimensions. Schizophr Res. 1997;23(1):15-23.

23. Morgan VA, Castle DJ, Jablensky AV. Do women express and experience psychosis differently from men? Epidemiological evidence from the Australian National Study of Low Prevalence (Psychotic) Disorders. The Australian and New Zealand journal of psychiatry. 2008;42(1):74-82.

24. Roy MA, Maziade M, Labbe A, Merette C. Male gender is associated with deficit schizophrenia: a meta-analysis. Schizophr Res. 2001;47(2-3):141-7.

25. Chang WC, Hui CL, Tang JY, Wong GH, Chan SK, Lee EH, et al. Impacts of duration of untreated psychosis on cognition and negative symptoms in first-episode schizophrenia: a 3-year prospective follow-up study. Psychol Med. 2013;43(9):1883-93.

26. Choi JS, Chon MW, Kang DH, Jung MH, Kwon JS. Gender difference in the prodromal symptoms of first-episode schizophrenia. Journal of Korean medical science. 2009;24(6):1083-8.

27. Mancevski B, Keilp J, Kurzon M, Berman RM, Ortakov V, Harkavy-Friedman J, et al. Lifelong course of positive and negative symptoms in chronically institutionalized patients with schizophrenia. Psychopathology. 2007;40(2):83-92.

28. Andreasen NC, Flashman L, Flaum M, Arndt S, Swayze V, 2nd, O'Leary DS, et al. Regional brain abnormalities in schizophrenia measured with magnetic resonance imaging. JAMA. 1994;272(22):1763-9.

29. Andreasen NC, Ehrhardt JC, Swayze VW, 2nd, Alliger RJ, Yuh WT, Cohen G, et al. Magnetic resonance imaging of the brain in schizophrenia. The pathophysiologic significance of structural abnormalities. Arch Gen Psychiatry. 1990;47(1):35-44.

30. Reite M, Sheeder J, Teale P, Adams M, Richardson D, Simon J, et al. Magnetic source imaging evidence of sex differences in cerebral lateralization in schizophrenia. Arch Gen Psychiatry. 1997;54(5):433-40.

31. Gur RE, Cowell PE, Latshaw A, Turetsky BI, Grossman RI, Arnold SE, et al. Reduced dorsal and orbital prefrontal gray matter volumes in schizophrenia. Arch Gen Psychiatry. 2000;57(8):761-8.

32. Gur RE, Turetsky BI, Cowell PE, Finkelman C, Maany V, Grossman RI, et al. Temporolimbic volume reductions in schizophrenia. Arch Gen Psychiatry. 2000;57(8):769-75.

33. Leung A, Chue P. Sex differences in schizophrenia, a review of the literature. Acta psychiatrica Scandinavica Supplementum. 2000;401:3-38.

34. Abel KM, Drake R, Goldstein JM. Sex differences in schizophrenia. International review of psychiatry. 2010;22(5):417-28.

35. Castle DJ, Murray RM. The neurodevelopmental basis of sex differences in schizophrenia. Psychol Med. 1991;21(3):565-75.

36. Lewine RR, Hudgins P, Brown F, Caudle J, Risch SC. Differences in qualitative brain morphology findings in schizophrenia, major depression, bipolar disorder, and normal volunteers. Schizophr Res. 1995;15(3):253-9.

37. Bogerts B, Ashtari M, Degreef G, Alvir JM, Bilder RM, Lieberman JA. Reduced temporal limbic structure volumes on magnetic resonance images in first episode schizophrenia. Psychiatry research. 1990;35(1):1-13.

38. Mancini-Marie A, Yoon U, Jiminez J, Fahim C, Potvin S, Grant JA, et al. Sex, age, symptoms and illness duration and their relation with gyrification index in schizophrenia. Clinical schizophrenia & related psychoses. 2015.

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

40. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. 1971;9(1):97-113.

41. Spitzer RL, Williams JB, Gibbon M, First MB. The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. Arch Gen Psychiatry. 1992;49(8):624-9.

42. Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. The Journal of clinical psychiatry. 2003;64(6):663-7.

43. Ashburner J. A fast diffeomorphic image registration algorithm. Neuroimage. 2007;38(1):95-113.

44. Ashburner J, Friston KJ. Computing average shaped tissue probability templates. Neuroimage. 2009;45(2):333-41.

45. Ashburner J, Friston KJ. Why voxel-based morphometry should be used. Neuroimage. 2001;14(6):1238-43.

46. Hurvich CM, Tsai CL. Model selection for extended quasi-likelihood models in small samples. Biometrics. 1995;51(3):1077-84.

47. Salgado-Pineda P, Caclin A, Baeza I, Junque C, Bernardo M, Blin O, et al. Schizophrenia and frontal cortex: where does it fail? Schizophr Res. 2007;91(1-3):73-81.

48. Dazzan P, Soulsby B, Mechelli A, Wood SJ, Velakoulis D, Phillips LJ, et al. Volumetric abnormalities predating the onset of schizophrenia and affective psychoses: an MRI study in subjects at ultrahigh risk of psychosis. Schizophr Bull. 2012;38(5):1083-91.

49. Hugdahl K, Loberg EM, Nygard M. Left temporal lobe structural and functional abnormality underlying auditory hallucinations in schizophrenia. Front Neurosci. 2009;3(1):34-45.

50. Williams LM. Voxel-based morphometry in schizophrenia: implications for neurodevelopmental connectivity models, cognition and affect. Expert Rev Neurother. 2008;8(7):1049-65.

51. Craig AD. Emotional moments across time: a possible neural basis for time perception in the anterior insula. Philos Trans R Soc Lond B Biol Sci. 2009;364(1525):1933-42.

52. Wotruba D, Heekeren K, Michels L, Buechler R, Simon JJ, Theodoridou A, et al. Symptom dimensions are associated with reward processing in unmedicated persons at risk for psychosis. Front Behav Neurosci. 2014;8:382.

53. Rolland B, Amad A, Poulet E, Bordet R, Vignaud A, Bation R, et al. Resting-state functional connectivity of the nucleus accumbens in auditory and visual hallucinations in schizophrenia. Schizophr Bull. 2015;41(1):291-9.

54. Supekar K, Menon V. Developmental maturation of dynamic causal control signals in higher-order cognition: a neurocognitive network model. PLoS computational biology. 2012;8(2):e1002374.

55. Cauda F, Cavanna AE, D'Agata F, Sacco K, Duca S, Geminiani GC. Functional connectivity and coactivation of the nucleus accumbens: a combined functional connectivity and structure-based meta-analysis. J Cogn Neurosci. 2011;23(10):2864-77.

56. Kurth F, Zilles K, Fox PT, Laird AR, Eickhoff SB. A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. Brain structure & function. 2010;214(5-6):519-34.

57. Mutschler I, Wieckhorst B, Kowalevski S, Derix J, Wentlandt J, Schulze-Bonhage A, et al. Functional organization of the human anterior insular cortex. Neuroscience letters. 2009;457(2):66-70.

58. Laruelle M, Abi-Dargham A. Dopamine as the wind of the psychotic fire: new evidence from brain imaging studies. Journal of psychopharmacology. 1999;13(4):358-71.

59. Seeman P. Schizophrenia and dopamine receptors. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2013;23(9):999-1009.

60. Hietala J, Syvalahti E, Vuorio K, Rakkolainen V, Bergman J, Haaparanta M, et al. Presynaptic dopamine function in striatum of neuroleptic-naive schizophrenic patients. Lancet. 1995;346(8983):1130-1.

61. Hutcheson NL, Clark DG, Bolding MS, White DM, Lahti AC. Basal ganglia volume in unmedicated patients with schizophrenia is associated with treatment response to antipsychotic medication. Psychiatry research. 2014;221(1):6-12.

62. Golkar A, Lonsdorf TB, Olsson A, Lindstrom KM, Berrebi J, Fransson P, et al. Distinct contributions of the dorsolateral prefrontal and orbitofrontal cortex during emotion regulation. PLoS One. 2012;7(11):e48107.

63. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception II: Implications for major psychiatric disorders. Biol Psychiatry. 2003;54(5):515-28.

64. Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD. Rethinking feelings: an FMRI study of the cognitive regulation of emotion. J Cogn Neurosci. 2002;14(8):1215-29.

65. Pena-Gomez C, Vidal-Pineiro D, Clemente IC, Pascual-Leone A, Bartres-Faz D. Down-regulation of negative emotional processing by transcranial direct current stimulation: effects of personality characteristics. PLoS One. 2011;6(7):e22812.

66. Kohn N, Eickhoff SB, Scheller M, Laird AR, Fox PT, Habel U. Neural network of cognitive emotion regulation--an ALE meta-analysis and MACM analysis. Neuroimage. 2014;87:345-55.

67. Smith R, Chen K, Baxter L, Fort C, Lane RD. Antidepressant effects of sertraline associated with volume increases in dorsolateral prefrontal cortex. J Affect Disord. 2013;146(3):414-9.

68. Heath RG, Franklin DE, Shraberg D. Gross pathology of the cerebellum in patients diagnosed and treated as functional psychiatric disorders. J Nerv Ment Dis. 1979;167(10):585-92.

69. Martin P, Albers M. Cerebellum and schizophrenia: a selective review. Schizophr Bull. 1995;21(2):241-50.

70. Andreasen NC, Pierson R. The role of the cerebellum in schizophrenia. Biol Psychiatry. 2008;64(2):81-8.

71. Andreasen NC, Shore D, Burke JD, Jr., Grove WM, Lieberman JA, Oltmanns TF, et al. Clinical phenomenology. Schizophr Bull. 1988;14(3):345-63.

72. Stoodley CJ, Schmahmann JD. Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. Cortex. 2010;46(7):831-44.

73. Laroi F, Woodward TS. Hallucinations from a cognitive perspective. Harv Rev Psychiatry. 2007;15(3):109-17.

74. Allen PP, Johns LC, Fu CH, Broome MR, Vythelingum GN, McGuire PK. Misattribution of external speech in patients with hallucinations and delusions. Schizophr Res. 2004;69(2-3):277-87.

75. Seal ML, Aleman A, McGuire PK. Compelling imagery, unanticipated speech and deceptive memory: neurocognitive models of auditory verbal hallucinations in schizophrenia. Cogn Neuropsychiatry. 2004;9(1-2):43-72.

76. Tracy DK, Shergill SS. Mechanisms Underlying Auditory Hallucinations-Understanding Perception without Stimulus. Brain Sci. 2013;3(2):642-69.

77. Sugimori E, Mitchell KJ, Raye CL, Greene EJ, Johnson MK. Brain mechanisms underlying reality monitoring for heard and imagined words. Psychol Sci. 2014;25(2):403-13.

78. Thoresen C, Endestad T, Sigvartsen NP, Server A, Bolstad I, Johansson M, et al. Frontotemporal hypoactivity during a reality monitoring paradigm is associated with delusions in patients with schizophrenia spectrum disorders. Cogn Neuropsychiatry. 2014;19(2):97-115.

79. Asami T, Hyuk Lee S, Bouix S, Rathi Y, Whitford TJ, Niznikiewicz M, et al. Cerebral white matter abnormalities and their associations with negative but not positive symptoms of schizophrenia. Psychiatry research. 2014;222(1-2):52-9.

80. Mazhari S, Moghadas Tabrizi Y. Abnormalities of mental rotation of hands associated with speed of information processing and executive function in chronic schizophrenic patients. Psychiatry Clin Neurosci. 2014;68(6):410-7.

81. Wang Q, Cheung C, Deng W, Li M, Huang C, Ma X, et al. Fronto-parietal white matter microstructural deficits are linked to performance IQ in a first-episode schizophrenia Han Chinese sample. Psychol Med. 2013;43(10):2047-56.

82. Tagamets MA, Cortes CR, Griego JA, Elvevag B. Neural correlates of the relationship between discourse coherence and sensory monitoring in schizophrenia. Cortex. 2014;55:77-87.

83. Yun JY, Hur JW, Jung WH, Jang JH, Youn T, Kang DH, et al. Dysfunctional role of parietal lobe during self-face recognition in schizophrenia. Schizophr Res. 2014;152(1):81-8.

84. Allen DN, Strauss GP, Barchard KA, Vertinski M, Carpenter WT, Buchanan RW. Differences in developmental changes in academic and social premorbid adjustment between males and females with schizophrenia. Schizophr Res. 2013;146(1-3):132-7.

85. Kulkarni J, Gavrilidis E, Hayes E, Heaton V, Worsley R. Special biological issues in the management of women with schizophrenia. Expert Rev Neurother. 2012;12(7):823-33.

86. Kulkarni J, Hayes E, Gavrilidis E. Hormones and schizophrenia. Curr Opin Psychiatry. 2012;25(2):89-95.

87. Sallet PC, Elkis H, Alves TM, Oliveira JR, Sassi E, Campi de Castro C, et al. Reduced cortical folding in schizophrenia: an MRI morphometric study. The American journal of psychiatry. 2003;160(9):1606-13.

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

89. Hoptman MJ, D'Angelo D, Catalano D, Mauro CJ, Shehzad ZE, Kelly AM, et al. Amygdalofrontal functional disconnectivity and aggression in schizophrenia. Schizophr Bull. 2010;36(5):1020-8.

90. Hoptman MJ, Volavka J, Johnson G, Weiss E, Bilder RM, Lim KO. Frontal white matter microstructure, aggression, and impulsivity in men with schizophrenia: a preliminary study. Biol Psychiatry. 2002;52(1):9-14.

91. Herbert MR, Ziegler DA, Makris N, Filipek PA, Kemper TL, Normandin JJ, et al. Localization of white matter volume increase in autism and developmental language disorder. Ann Neurol. 2004;55(4):530-40.

92. Garcia-Marti G, Aguilar EJ, Lull JJ, Marti-Bonmati L, Escarti MJ, Manjon JV, et al. Schizophrenia with auditory hallucinations: a voxel-based morphometry study. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(1):72-80.

93. Neckelmann G, Specht K, Lund A, Ersland L, Smievoll AI, Neckelmann D, et al. Mr morphometry analysis of grey matter volume reduction in schizophrenia: association with hallucinations. Int J Neurosci. 2006;116(1):9-23.

94. Gaser C, Nenadic I, Volz HP, Buchel C, Sauer H. Neuroanatomy of "hearing voices": a frontotemporal brain structural abnormality associated with auditory hallucinations in schizophrenia. Cerebral cortex. 2004;14(1):91-6.

95. Aguilar EJ, Sanjuan J, Garcia-Marti G, Lull JJ, Robles M. MR and genetics in schizophrenia: focus on auditory hallucinations. Eur J Radiol. 2008;67(3):434-9.

96. Fahim C, Stip E, Mancini-Marie A, Gendron A, Mensour B, Beauregard M. Differential hemodynamic brain activity in schizophrenia patients with blunted affect during quetiapine treatment. Journal of clinical psychopharmacology. 2005;25(4):367-71.

97. Fahim C, Stip E, Mancini-Marie A, Mensour B, Boulay LJ, Leroux JM, et al. Brain activity during emotionally negative pictures in schizophrenia with and without flat affect: an fMRI study. Psychiatry Res. 2005;140(1):1-15.

98. Stip E, Fahim C, Liddle P, Mancini-Marie A, Mensour B, Bentaleb LA, et al. Neural correlates of sad feelings in schizophrenia with and without blunted affect. Can J Psychiatry. 2005;50(14):909-17.

99. Stip E, Fahim C, Mancini-Marie A, Bentaleb LA, Mensour B, Mendrek A, et al. Restoration of frontal activation during a treatment with quetiapine: an fMRI study of blunted affect in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2005;29(1):21-6.

Table 1. Demographics of schizophrenia patients

	SZ-M Mean (SD)	SZ-F 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

Table 2. Regions of gray and white density differences between the schizophrenia group and healthy 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 rectal	130	4.12 (-6, 21, -23)
	Posterior parietal	138	3.72 (-9, -48, 66)

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

GMD	Region	K	T	MNI
PANSS positive	L Insula	523	4.68	-42, -42, 18
	R Caudate	195	4.21	35, -16, -9
PANSS negative	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	R Middle frontal	240	3.82	27, 57, -8
PANSS negative	R superior frontal	72	4.32	14, 56, 24

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

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

Table 5. Clinical assessments in schizophrenia patients

	SZ-M	**SZ-F**	**P value**
	Mean (SD)	**Mean (SD)**	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

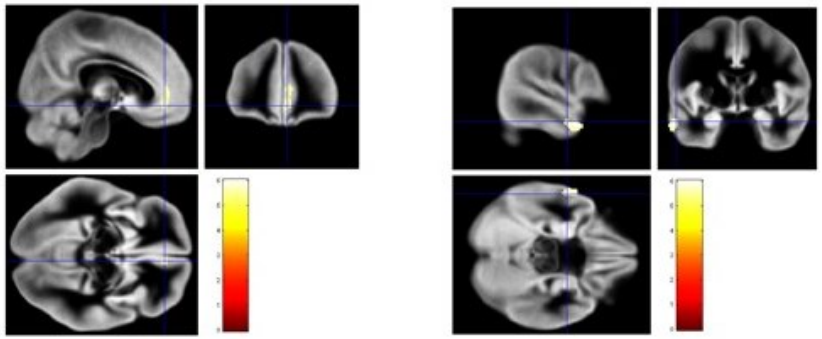
Lack of judgment and insight	2.83 (0.79)	2.93 (1.73)	0.819
Disturbance of volition	2.44 (1.10)	2.88 (1.15)	0.272
Poor impulse control	2.44 (0.92)	2.75 (1.34)	0.440
Preoccupation	2.17 (0.86)	2.62 (0.96)	0.151
Active social avoidance	2.94 (1.21)	3.19 (1.47)	0.601

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

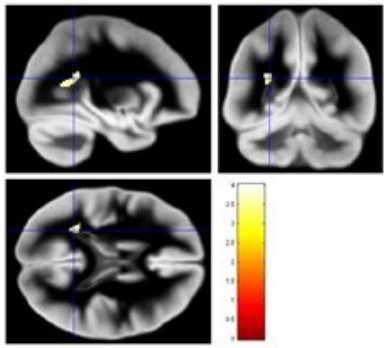
	NC		SZ		P value df=77
	Mean	**SD**	**Mean**	**SD**	
Block design from WAIS-III	12.03	3.289	9.12	3.198	0.001
Similitudes from WAIS-III	11.36	2.653	7.27	2.293	0.001
Vocabulary from WAIS-III	10.44	2.259	6.24	2.465	0.001
Raven percentile	80.56	18.320	50.99	24.827	0.001
Years of education	18.41	3.88	11.72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

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.

GMD: NC minus SZ
frontal & temporal



GMD: SZ minus NC
posterior cingulate



WMD: NC minus SZ
frontal & parietal

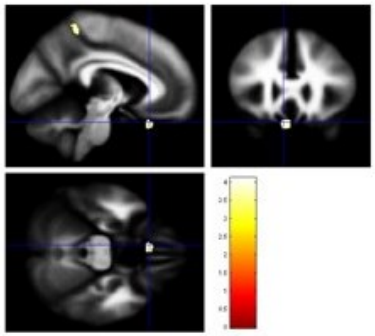
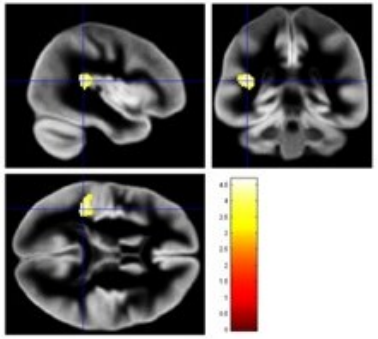


Figure 2. Positive correlations between GMD and WMD regression analysis based on symptoms

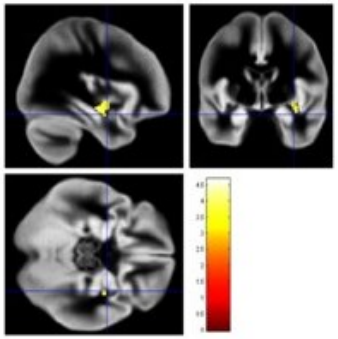
PANSS positive

GMD L Insula



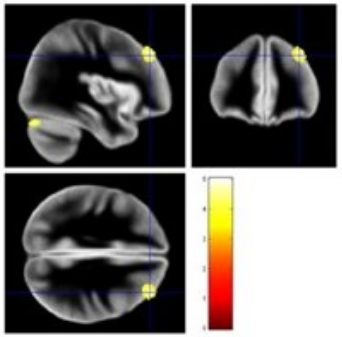
PANSS positive

GMD R caudate



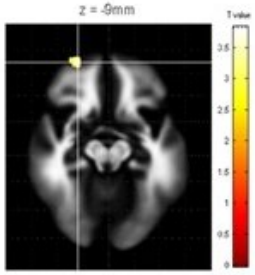
PANSS negative

GMD R middle frontal and R cerebellum



PANSS positive

WMD R middle frontal



PANSS negative

WMD R superior frontal

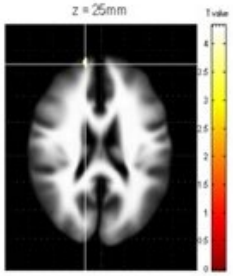


Figure 3. Negative correlations between GMD and WMD regression analysis based on symptoms

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

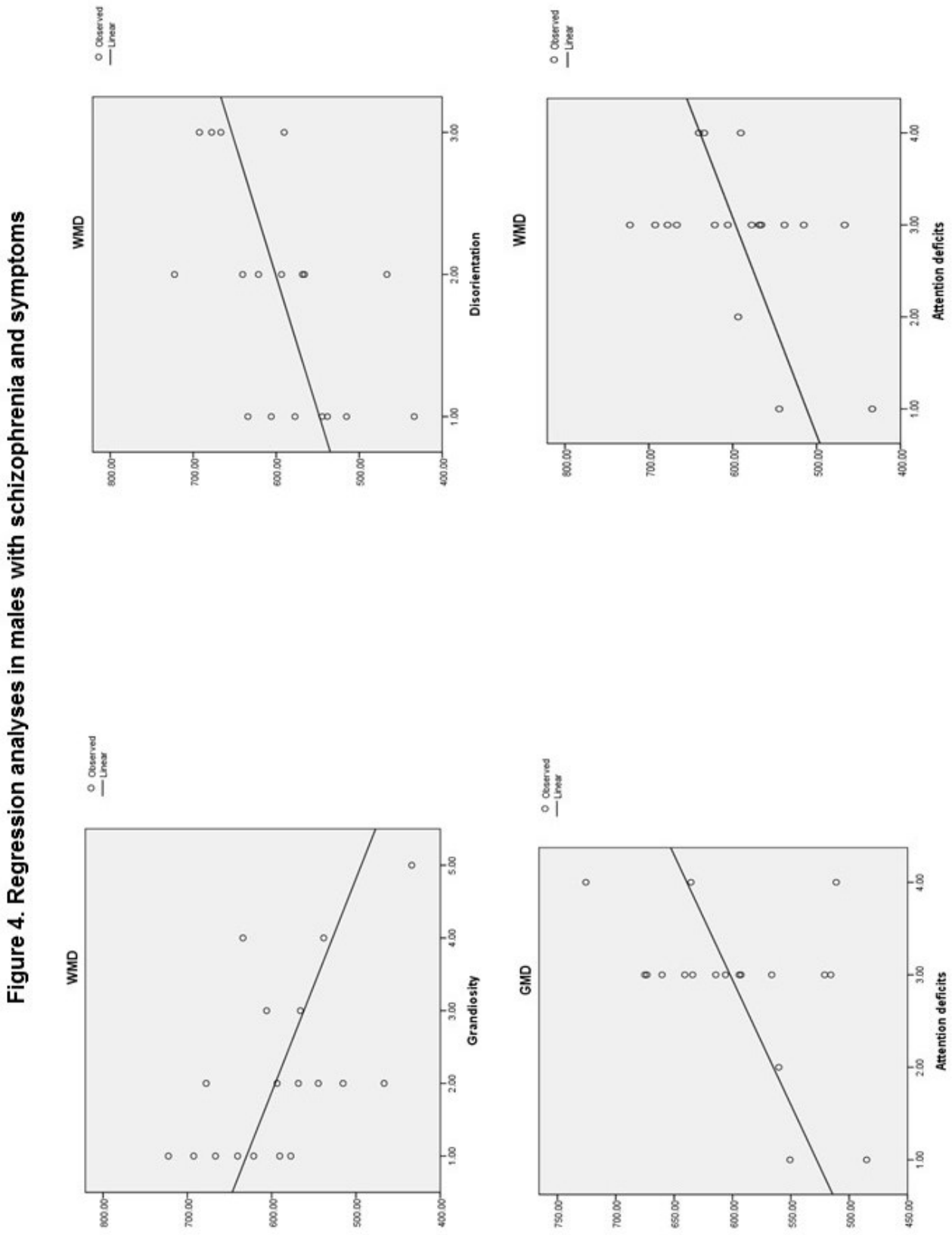
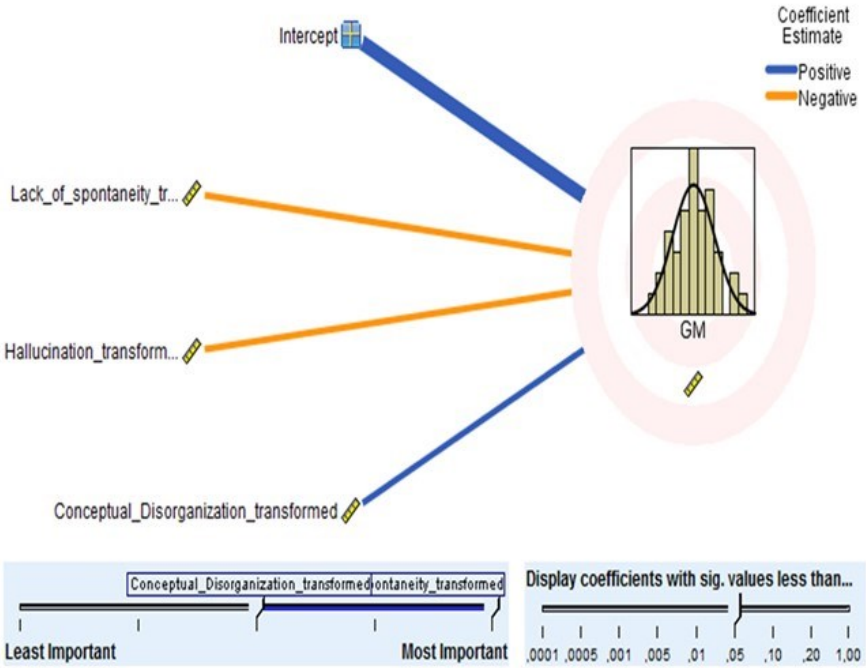


Figure 4. Regression analyses in males with schizophrenia and symptoms

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

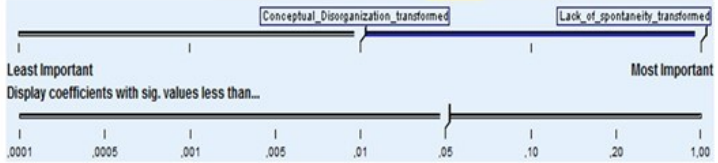


Figure 6. Model prediction by importance: ALM grey matter results

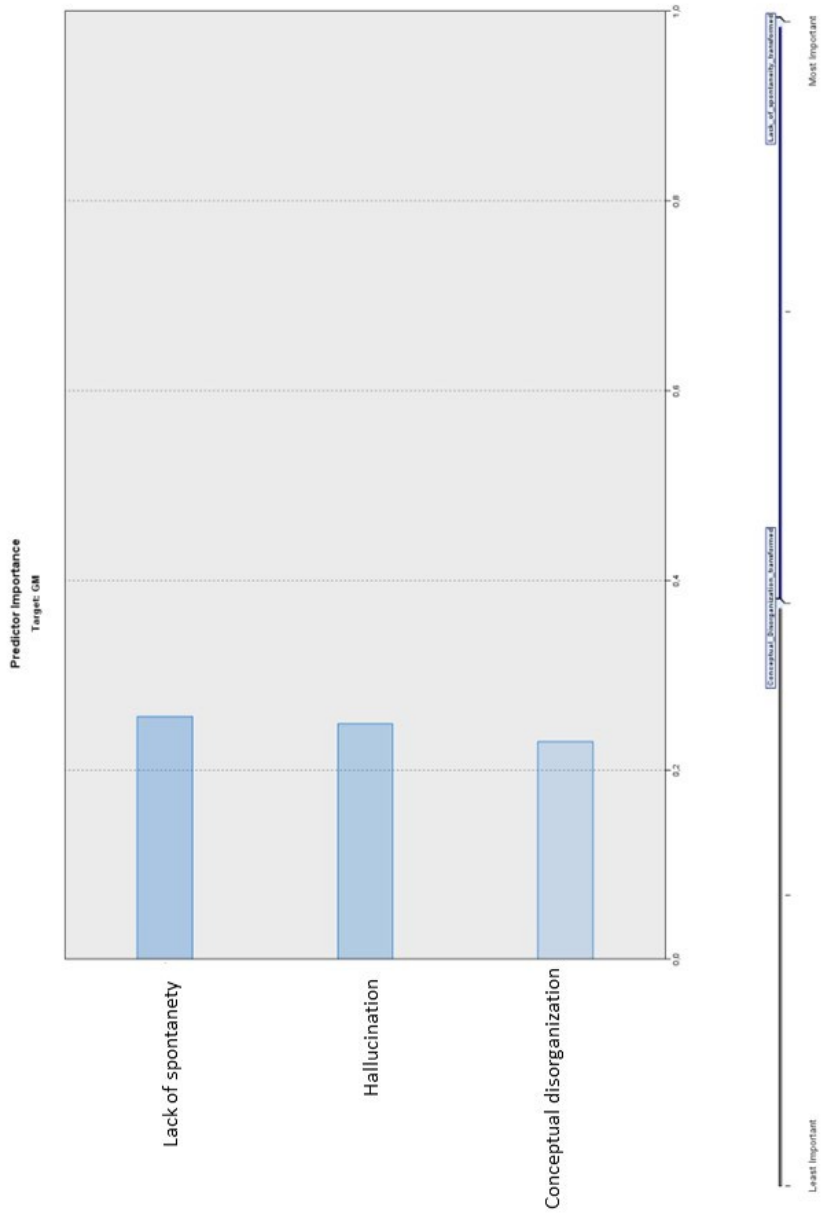
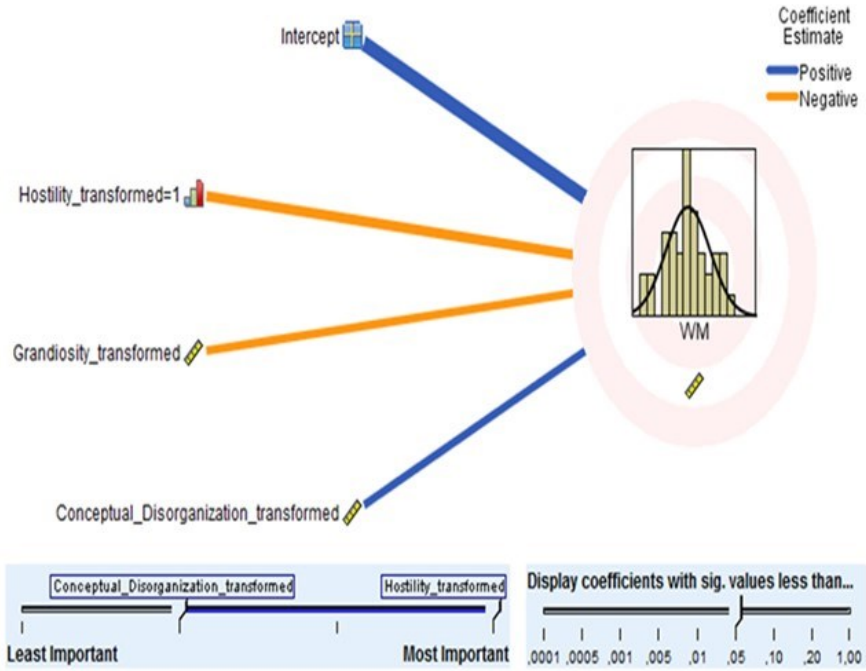


Figure 7. Model prediction by importance: ALM results
Coefficients
Target: White Matter Densities



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				

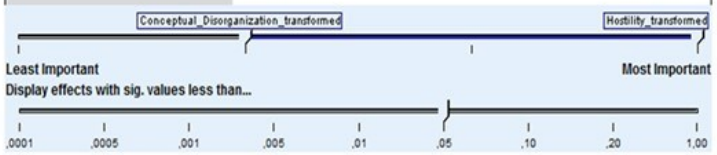


Figure 8. Model prediction by importance: ALM white matter results

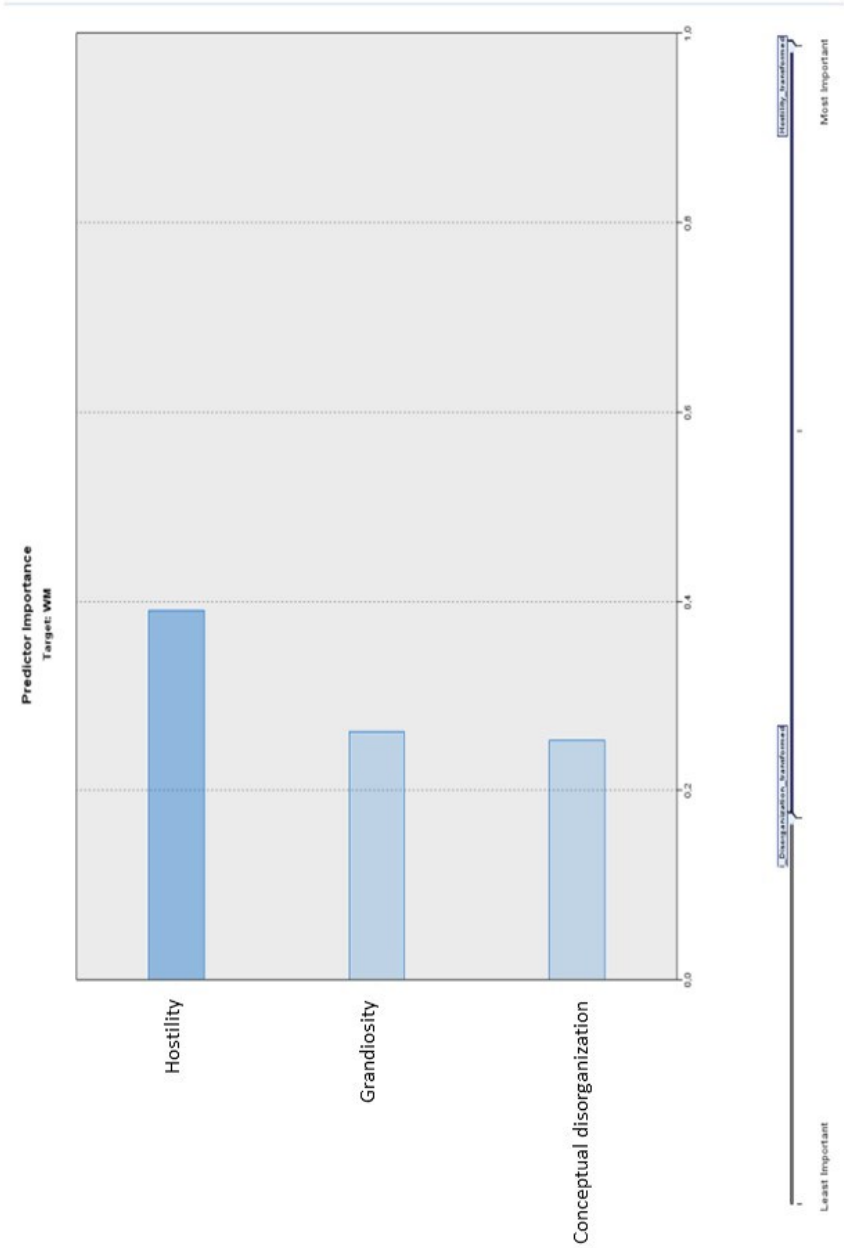


Table and figure legends

Figure 4. Regression analyses in males with schizophrenia and symptoms

In SZ-M inverse correlation between ideas of grandiosity and WMD (r=.551, r2=.303, t=-2.639, p=.018) were found. Positive correlations were also found 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).

Figure 5. Model prediction by importance: ALM results

The ALM predicted the continuous target (GMD) 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 GMD. Conceptual disorganization predicted increased GMD.

Figure 7. Model prediction by importance: ALM results

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

7 Article 3

The following work has been submitted and accepted provided revision in *Schizophrenia Research*. Resubmission of revised version will before the end of September 2016 under the title: "*The basis of memory accuracy in schizophrenia: a combined gray and white matter DARTEL voxel-based morphometry"*.

The third paper shifts away from symptoms to other core aspects of schizophrenia: cognition and emotion. Our group has extensively investigated sex differences in cognition and emotion in schizophrenia using functional imaging. Sex differences were consistently found. It was of interest to further investigate if such functional brain differences are also present on a morphological level. From a neurodevelopmental point of view, morphological brain changes require more time to manifest alterations. Brain functionality may be influenced by transient changes (e.g. stress). Here, sex differences reappear significantly. In this study, total white matter density in schizophrenia males correlated negatively with memory accuracy of positive and negative images. These correlations were observed only in male patients but not in females.

The basis of memory accuracy in schizophrenia: a combined gray and white matter DARTEL voxel-based morphometry

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Abstract

Introduction: There is robust evidence of the influence of emotion on cognition and vice versa. In addition, schizophrenia positive and negative symptoms are hypothesized to be related to abnormal threat-processing affecting cognitive domains. This study investigated cerebral structures associated with cognitive-memory accuracy for positive (PMA), negative (NMA) and neutral (ZMA) emotions.

Methods: Patients with schizophrenia (SZ) (N=40) and normal controls (NC) (N=40) matched for age and sex were assessed for memory accuracy using the IAPS images. Results were correlated with cerebral gray matter densities (GMD) and white matter densities (WMD) using voxel-based morphometry (VBM) on T1-3T MRI.

Results: Compared to NC, patients had decreased correlations with memory performance in a number of areas: GMD of the posterior/postcentral parietal, lentiform/putamen/caudate and inferior frontal/orbital cortex and WMD of the postcentral parietal and performance on the NMA; GMD of the temporal lobe/fusiform and WMD of the inferior temporal, precuneus parietal and frontal lobe and performance on the PMA; GMD of the cerebellum (anterior lobe) and WMD of the middle temporal and performance on the ZMA. In addition, SZ had increased correlations in the GMD and WMD of the inferior occipital cortex and the lingual occipital region respectively with performance on the NMA; increased correlation in WMD of the angular parietal region with performance on PMA; and WMD of the superior temporal region with performance on ZMA. Sex differences were observed, such that male patients' total WMD inversely correlated with performance on NMA and PMA, and no significant correlations were found in females.

Conclusion: Findings support the fronto-temporal regional atrophy hypothesis in schizophrenia. Relatively increased occipito-parietal WMD in patients advances the hypothesis that the core pathophysiological problem underlying recall memory in SZ may be related to disruptive coordination of large-scale brain networks. This may be affected by structural deficits more evident in male patients. This latter result implies that most of the significant findings in the entire group of schizophrenia patients might be driven by males, but more participants would have to be tested to verify this supposition.

Keywords: Schizophrenia, memory, positive emotion, negative emotion, neutral emotion, gray matter, white matter, voxel based morphometry.

1. Introduction

Schizophrenia is a term created by Bleuler in 1911 to describe the fragmentation and disintegration of the mind and behavior as the essence of this devastating disorder (1). Since then, research has intensively investigated the splitting of thoughts, feelings, and actions in schizophrenia (2-6). Specifically, studies addressed how and why these functions are dissociated (7-9). Although there is robust evidence of the influence of emotion on cognition and vice versa, the nature of these interactions and their role in psychotic symptoms are not yet clearly explained. Neurocognitive research indicates that emotion affects memory processes (10-12). Moreover, it has long been known that schizophrenia is associated with chronic presence of negative and positive symptoms, hypothesized to relate to abnormal threat processing affecting cognitive domains (13-16). Memory deficits are among the most common in schizophrenia and have widespread impact on cognition in general. This being said, we note that the neurobiological underpinnings of the relationship between emotion processing and cognition merit more attention than it has received.

Recently, an elegant review argued that alteration of the basic sense of self-awareness might be an essential distortion of schizophrenia (17). The authors placed further stress on the role of distortion of social skills and proposed what they referred to as the "triple brain network model of the dysfunctional switching between default mode and central executive network related to the aberrant activity of the salience network". Schizophrenia has also been proposed to result from a dysfunction in context processing and self-processing (18, 19). Clearly, memory dysfunction and its interaction with emotion processing, plays an important role in these models. Additionally, schizophrenia patients display deficits in memory processes known as retrospection and imagination (20). They may construct unusual beliefs or illusions (confabulation) when a stimulus has not been presented previously but recalled incorrectly or falsely (21). For example, in prediction-error-related brain responses patients show cortical activation in frontal lobe during disrupted prediction-error processing and construction of delusions, suggesting that patients with schizophrenia have an inappropriate representation of the world using extraneous information (22).

Overall, according to these theories, schizophrenia patients have major difficulties in projecting themselves into past and future events, probably because of difficulties in retrieving circumstantial information from previous events. Hence, constructing strategic representations and

experiencing a continuity of subjective time becomes essentially very difficult. Such neurocognitive malfunction renders memory accuracy inefficient (18-20). Corlett et al., (2009) argue that certain experiences are inappropriately surprising and require an explanation. When the surprising experience is repeated, that explanation develops into an unusual or inappropriate belief (21).

Neuroimaging studies have extensively investigated memory accuracy in schizophrenia (23-31). In a functional neuroimaging study, Sergerie and colleagues (2010) compared emotional memory recognition in schizophrenia patients with healthy subjects. The researchers observed that despite an overall lower memory accuracy, emotional memory was intact in schizophrenia. This pattern was present despite the fact that emotion-specific differences in brain activation exist between patients and controls, possibly reflecting different strategies (32). Wolf and colleagues (2011) compared accurate responses during a working memory task for emotional faces between a homogeneous group of high-performing patients and a control group. The authors confirmed previous findings showing a correlation between WM performance with alternating activity in the left and right prefrontal cortex. Furthermore, they found enhanced activity in higher visual areas of patients during encoding and maintenance (33). Another study argued that the precuneus and cerebellum function contribute to a better performance on working memory and preserved insight in schizophrenia via compensatory neural activity in the frontal cortex and cerebellum (34). More recently, a study on working memory in schizophrenia concluded that the draining of interference-control processes results in reduced behavioral performance (35) Specifically, proactive inhibitory deficits and impaired control over memory was present in schizophrenia patients who were relying on reactive interference-control processes and manifested reduced behavioral performance (35). When considering structural gray and white matter neuroimaging studies, temporal lobe neuroanatomical abnormalities remain among the most robust findings in schizophrenia (36-40). The temporal lobe, in turn plays a critical role in memory (15, 27, 41)

Overall, it is well established that memory deficits in schizophrenia represent core endophenotypes because they are common, relatively stable across the course of the illness, are present regardless of the presence of fluctuating psychotic symptoms, and are found to a lesser degree in unaffected relatives (42). Importantly, lack of responsiveness of memory deficits to current typical and/or atypical antipsychotic medication call for further investigation to elucidate these deficits and their relation to brain morphology in schizophrenia.

Several studies have reported sex differences in cognitive performances in normal populations (43-47). These sex differences seem to be more prominent in schizophrenia patients. Several studies show that males and females with schizophrenia both have cognitive impairments but in different cognitive domains (48-54). For example, males with schizophrenia had significantly more serious cognitive deficits than female patients in immediate and delayed memory, but not in language, attention, or visuo-spatial processing (55). Neural substrates during cognitive tasks also show sex-dependent difference in patients with schizophrenia. Our group found that female patients had decreased brain activations in the middle cingulate gyrus and amygdala during recognition of negative images and decreased activations during the positive condition in the middle and inferior frontal gyrus. Conversely, male patients had increased activations compared to the same-sex controls in the medial prefrontal gyrus during recognition of negative stimuli and in the parietal, temporal and limbic structures during the recognition of positive pictures (56).

Taking previous studies into consideration, the purpose of the present study was to characterize the association between memory accuracy and anatomical GMD and WMD in schizophrenia patients. In addition, we examined potential sex-dependent differences using optimized voxel-based morphometry. We hypothesized that patients would show performance deficits in relation to abnormalities in their structural GM and WM in several regions underlying memory recall in schizophrenia.

2. Methods

2.1 Participants

Eighty-one subjects were included in this study: 41 (22 males [NC-M] and 19 females [NC-F]) normal controls (NC) and 40 DSM-IV schizophrenia patients (SZ) (20 males [SZ-M] and 20 females [SZ-F]) (57). 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) (58) 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, no significant differences were found between male groups or female group. 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).

All patients were re-evaluated by experienced psychiatrists before being assigned to the research group. Affective, schizoaffective, and schizophreniform psychoses were excluded. Control participants were screened with the non-patients edition of the Clinical Interview for DSM-IV (SCID) (59). Symptom severity was rated according to the positive and negative syndrome scale (PANSS) (60). 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 as bipolar disorder, personality disorder, etc., therefore a psychiatric consultation favors a better diagnosis. All the patients received at least one atypical antipsychotic (chlorpromazine equivalence was calculated) (61) (Table 1.).

----------Insert Table 1 around here---------

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

2.2 Behavioral memory task

First, participants passively viewed negative, positive, and neutral pictures taken from the International Affective Picture System (IAPS) while in the scanner (62). Although participants were aware that a memory task would follow, they were not explicitly told to remember the images. After a 15-min delay, participants performed the memory task, consisting of viewing blocks of positive, negative, and neutral pictures similarly to the incidental encoding task. Half of the stimuli in each block originated from the incidental-encoding task while the other half were never seen before. During this memory task, participants were asked to determine, by pressing the correct button, which of the stimuli were previously seen. To assess the participants' subjective emotional responses, immediately at the end of the session, participants were again presented with the image blocks and were asked to rate them as a whole on a scale ranging from zero (absence of any emotional reaction) to eight (strongest emotion ever felt in one's lifetime) the intensity of experienced emotion. For fMRI results please refer to Bourque et al., (2013), Lakis et al., (2012) and Lakis et al., (2013) (63-65).

Additional neuropsychological Cognitive evaluations were performed on patients and controls using WAIS-III and Raven percentile tests. Neuropsychological tests were analyzed using SPSS21 version to perform ANOVA and Bonferroni multiple group comparisons ($p<0.05$) for the WAISS-III and Raven percentile tests.

2.3 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.

2.4 Image 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 the latest version of SPM8. All participants passed the SPM8 data quality control. Images were analyzed using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) toolbox in the latest version of SPM8 used for voxel-based morphometry (VBM). We used VBM to assess the voxel-wise comparison of the local concentration of gray and white matter between NC and SZ.

DARTEL toolbox uses a high dimensional warping process that increases the registration between individuals, which results in improved localization and increased sensitivity in analyses (66). 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 then 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. Following these steps, the normalized gray matter (GM) and white matter (WM) maps were modulated with the resulting Jacobian determinant maps and smoothed with an 8-mm FWHM Gaussian kernel. Total GMD, WMD and brain volumes were obtained using 'calculate raw volumes' in the VBM8 toolbox. The segmented images were visually inspected, then, imported to DARTEL for the 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) (66, 67) 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 that are significantly related to a specific variable (68). VBM is not biased to one particular structure, which permits an even-handed and comprehensive assessment of anatomical differences throughout the brain (68). Using the tool

Talairach Applet http://www.talairach.org/applet.html the anatomic location of significant clusters was detected. The resulting sets of voxels from each contrast represent a statistical parametric map of the t-statistic (SPM-t). We excluded all voxels with gray matter values of less than 0.01 (absolute threshold masking). For all statistical analyses of VBM data, we used a uniform threshold of $p < 0.001$ (uncorrected) and a minimum cluster size threshold of 100 voxels has been introduced for each contrast. This threshold is equivalent to a map-wise false positive rate of alpha < 0.0001 using a Monte Carlo procedure as implemented in the AlphaSim program in the Analysis of Functional Neuroimages software package (69, 70). Using SPM DARTEL factorial design specification we conducted an ANCOVA analysis between SZ and NC considering memory accuracy for negative, positive, and neutral recall scores as covariates.

2.5 Group comparisons

ANCOVA was applied to investigate differences in memory accuracy between groups. This analysis considered diagnostic group (SZ vs NC) by memory condition (positive, negative, neutral) interaction, as well as the main effect of group and condition.

The primary focus of the analyses was the relationship between GMD and WMD (as derived from VBM) with memory accuracy. As SZ differed from NC in total GMD and duration of education, we calculated contrasts between SZ and NC with whole brain ANCOVAs, including total and regional GMD and WMD and duration of education as covariates.

3. Results

3.1 Neuropsychological tests

ANOVA revealed significant group differences in all sub categories of the WAIS-III test where NC-M significantly out-performed SZ-M on all subcategories of the WAIS-III and Raven percentile tests. In female groups, NC-F out performed SZ-F on the Raven percentile and only two categories of the WAIS-III (Similitudes from WAIS-III and Vocabulary from WAIS-III). No differences were found on Block design when comparing female groups. No significant sex differences were found between normal control groups, while in patients, females out performed

males on the Raven percentile task (males=42.18, SD=22.54; females=60.23, SD=24.27, p=0.024, df=38) (Table 2).

----------Insert Table 2 around here---------

3.2 Structural and Behavioral results as assessed by VBM8

The analysis probing relationship between VBM and task performance showed correlations significant correlations in NC between NMA and GMD in the right posterior parietal cortex, lentiform, putamen, and caudate; and the left inferior orbitofrontal cortex. In SZ, correlations were observed between NMA and GMD in the left inferior occipital cortex. NC also showed significant correlations between PMA and GMD in the left temporal and fusiform gyrus, as well as between ZMA and the left anterior cerebellum. SZ did not show any correlation between GMD and PMA or ZMA. Correlation between Compared to SZ, WMD were higher in NC in the left postcentral parietal region for NMA, the left inferior temporal, left precuneus parietal, and left frontal regions for PMA, and left middle temporal region for ZMA. SZ had more correlations between WMD in left lingual occipital region and NMA; the left angular parietal region and PMA and the right superior temporal region for ZMA (please see Table 3, Figure 1 and 2).

----------Insert Table 3 and Figure 1 and 2 around here---------

3.3 Structural, behavioral and demographic results as assessed by SPSS21

Behaviorally we found no significant (two-tailed) differences between SZ and NC in respect to age (F=0.31; t=-0.34; p<0.74, df=77), sex (F=0.21; t=-0.32; p<0.75, df=77), WMD (F=0.19; t=-0.58; p<0.56) or total brain volume (F=0.01; t=0.52; p<0.60, df=77). We found a significant (two-tailed) group difference where NC had higher GMD than SZ (F=2.17; t=2.13; p<0.03). ANCOVA also revealed significant group differences where NC had better NMA (F=7.10; t=4.06; p<0.001, df=77), PMA (F=15.62; t=5.75; p<0.001, df=77) and ZMA (F=9.03; t=6.56; p<0.001, df=77) (Figure 4 and 5).

----------Insert Figure 4 and 5 around here---------

3.4 Sex differences

3.4.1 Memory performance

Behaviorally, NC-M performed better on memory accuracy than SZ-M and NC-F performed between than SZ-F on all conditions (positive, negative, and neutral) (Table 4). There were no significant sex differences in performance on any of the three memory conditions (positive, negative or neutral) in controls or in patients.

----------Insert Table 4 around here---------

3.4.2 Subjective rating

Subjective rating of images showed intriguing results. NC-M had lower subjective scores for negative and positive images compared to NC-F (respectively NC-M=5.04, SD=1.06, NC-F=5.83, SD=0.60, p=0.007, df=77 and NC-M=4.38, SD=1.14, NC-F=5.12, SD=0.92, p=0.032, df=77). Significant differences were observed between NC-F and SZ-F, where SZ-F were less emotionally affected by negative images (SZ-F=5.14, SD=1.24, NC-F=5.83, SD=0.60, p=0.035, df=77). There were no significant differences is subjective rating between male groups, however SZ-M showed a trend, such that they had higher subjective scores for neutral images (NC-M=1.13, SD=1.11, SZ-M=2.10, SD=1.60, p=0.066, df=77). In addition, SZ-M had significantly higher rating scores for neutral images compared to NC-F (SZ-M=2.10, SD=1.60, NC-F=1.07, SD=0.80, p=0.037, df=77). No significant differences in ratings were found between females with schizophrenia and normal control males.

3.4.3 Correlations

Sex differences were observed. Specifically in SZ-M inverse correlations were found in WMD and NMA (r=.470, r2=.221, t=-2.258, p=.037, df=40) and PMA (r=.439, r2=.193, t=-2.074,

p=.05, df=40). In NC-M, GMD positively correlated with NMA (r=.444, r2=.198, t=2.219, p=.038, df=40). No correlations were observed in female groups (Figure 6).

----------Insert Figure 6 around here---------

4. Discussion

The current study aimed to test whether patients with schizophrenia would differ in terms of behavioral results, as well as GMD and WMD, from normal controls as assessed by memory accuracy and voxel-based morphometry. As hypothesized, SZ patients performed significantly worse on the memory accuracy task and had significantly decreased GMD and WMD in brain regions associated with the behavioral task, relative to NC. Memory accuracy scores for the negative, positive and neutral IAPS images were used as covariates in the structural brain analyses to identify brain regions within which GMD and WMD correlated with behavioral performance. Overall, the findings broadly implicated abnormalities of association between memory accuracy and brain GMD and WMD in schizophrenia.

Normal controls showed significant correlations with memory accuracy in the GMD of several regions: posterior parietal, putamen, caudate, frontal, temporal and cerebellum, compared to patients. Several studies show structural and functional abnormalities in these regions in patients with schizophrenia (71-76). Patients showed correlation in GMD in the inferior occipital cortex specifically for memory accuracy of negative images. Special attention to the GMD and WMD in the posterior parietal region is warranted, as this region strongly differentiated NC from SZ in relation to the memory recall scores. The posterior parietal region is particularly engaged in visuospatial attention and memory (77), and several studies have reported gray matter abnormalities as reversed asymmetry (78), reduced gray matter density (79), and impaired activity during memory retrieval tasks (80, 81) in schizophrenia. We observed that SZ displayed a relationship between the memory score accuracy recall and the WMD of the angular region, which is also situated in the parietal lobe. The angular region is a heteromodal region involved in verbal retrieval, language and semantic processing (82) and spatial attention and orienting (83). According to Pearlson et al., (1996) (84), schizophrenia is associated with disturbance in the heteromodal

cortex which is considered as "higher-order parallel distributed networks of circuits, mediating complex representationally guided behaviors".

Compared to schizophrenia patients, Normal controls showed significant correlations between the temporal lobe and memory accuracy. This finding is in accordance with the literature showing that abnormalities in this region are associated with cognitive deficits (85). Unlike normal controls in this study, patients did not show any significant correlations between the cerebellum and memory accuracy. 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 (86).

The most significant result is the increased GMD and WMD in parieto-occipital regions in SZ compared to NC in relation to performance on the memory task. This finding is in agreement with previous studies showing that patients with schizophrenia engage both higher visual and sensory functions to a much greater extent than controls during memory performance (33). Along with our results, in their review, Crossley and colleagues (2014) stated that lesions in schizophrenia were concentrated in both frontal and temporal cortical hubs (87).

The evidence points to significantly more correlations with GMD in NC than SZ, which is in accordance with the broad body of literature we presented in the introduction. We did not find the same result regarding WMD. Additionally, SZ displayed stronger correlations between WMD regions (i.e., parietal and occipital) and memory accuracy. We posit that the relatively late WM myelination and neuronal pruning of brain regions in schizophrenia might play a role in our findings (88-90). In addition, it has also been suggested that schizophrenia is a consequence of a neurodevelopmental process of synaptic overpruning (91).

Most neuroimaging studies on memory in schizophrenia have focused on working memory during a functional magnetic resonance imaging. Considering a strong relationship between brain function and structure (92) we attempted to investigate the core GM and WM structures in relation to the memory deficits, which are among the core endophenotypes in schizophrenia (93). Interpreting reality mostly involves remembering relative information about a situation. Therefore, understanding recall and overall memory dysfunction in schizophrenia is fundamental. For example, when remembering that "I was in my friends' house yesterday", a firm grounding in reality requires that I know the context in which that memory was formed

As hypothesized, sex differences were observed in the correlation between structural abnormalities and memory performance. Behaviorally, normal control males significantly out-performed 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 no differences were found between female groups on the block design task. When direct comparisons were performed 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 (94, 95). Studies on healthy population show better performances in males compared to females on spacio-visual tasks (96, 97). Together these findings support the presence of an inverse sexual dimorphism in schizophrenia patients (98-100).

Behaviorally, both females and males with schizophrenia performed worse than same-sex control groups on all conditions of the memory task, but no sex differences were observed in controls or in patients. This was an unexpected finding, since we anticipated that females and males with schizophrenia would perform differently; specifically that male patients would show greater deficits. We propose that the emotional component of this task played a role in decreasing the anticipated performance in female patients. We can find support for this postulation when analysing the subjective rating results. Here clearly we observe that females with schizophrenia expressed less subjective experience to negative images compared to the same-sex controls. Additionally, difference in subjective rating disappeared when we compared females with schizophrenia and normal control males. Most studies show no sex differences in emotional experience (101-103). Thus, our finding that female patients report less subjective experience with negative images is relatively novel. Here, we observe again an inverse sexual dimorphism in female patients with schizophrenia. In our study, males with schizophrenia subjectively rate negative images similarly to normal control males, but rated neutral images greater than both males and females controls. A meta-analyses by Cohen and Minor (2010) revealed that schizophrenia patients had preserved emotional experience but may experience strong aversive emotions when processing stimuli considered by healthy population as pleasant or neutral (101).

To explain our findings, we postulate that as a way of coping with the disorder, females with schizophrenia use stress avoidance strategies to prevent exacerbation of symptoms. Studies demonstrate that patients who manage stressful events and internal stress are less likely to present sever symptoms (104). Emotion-focused and inhibitory coping styles against stress have been reported in healthy females more than males who use more operative coping styles (105, 106). Interestingly, male patients in our study over experienced neutral images.

In this study, total WMD in males with schizophrenia correlated negatively with memory accuracy of positive and negative images. These correlations were observed only in male patients but not in females. We did not perform regions of interest analysis, which is a subject of a future study. Highly et al., (2003) has reported distinct sex difference in schizophrenia patients, where female patients had reduced white matter volumes in the occipito-parietal region, while male patients had increased density in the same region (107). Of interest, in our study we found abnormalities in white matter densities in the same region in our group of schizophrenia patients. Further investigation is needed to find out if these differences are sex specific.

Despite diligence in matching our groups for sex and age, other potential confounds including age at onset, length of medication exposure and progressive GM changes in schizophrenia may have affected our results. Another shortcoming is that the DARTEL VBM study cannot be used to directly infer GM-WM connectivity and projections, and thus our data does not immediately address the question of whether schizophrenia patients alternatively use occipito-parietal network instead of fronto-parietal network (i.e., rearranged connections). Hence, future studies are needed to differentiate network dysfunction from previously observed GM and WM abnormalities of the fronto-temporal, occipito-parietal and cerebellar-fronto hubs, and to link such disturbed connectivity patterns with specific clinical and cognitivo-behavioral phenotypes of schizophrenia.

Overall, our findings may help to elucidate key cortical regions implicating loss of GM/WM volume/density, which may play a role in the disturbed cerebral connectivity network needed for efficient memory recall in schizophrenia. In agreement with Wang et al., (2010) (108), our findings suggest that the core pathophysiological problem underlying symptom presentation and cognitivo-emotional processes are related to disruptive coordination of large scale brain networks and this may be affected by structural deficits. These structural deficits are strongly differentiated by sex.

References

1. Bleuler E. Dementia Praecox or the Group of Schizophrenias. . (translated by J Zinkin, published in 1950) 1950.
2. Antonova E, Kumari V, Morris R, Halari R, Anilkumar A, Mehrotra R, et al. The relationship of structural alterations to cognitive deficits in schizophrenia: a voxel-based morphometry study. Biol Psychiatry. 2005;58(6):457-67.
3. Rapoport JL, Giedd JN, Gogtay N. Neurodevelopmental model of schizophrenia: update 2012. Molecular psychiatry. 2012;17(12):1228-38.
4. Garrity AG, Pearlson GD, McKiernan K, Lloyd D, Kiehl KA, Calhoun VD. Aberrant "default mode" functional connectivity in schizophrenia. The American journal of psychiatry. 2007;164(3):450-7.
5. Hemsley DR. The development of a cognitive model of schizophrenia: placing it in context. Neurosci Biobehav Rev. 2005;29(6):977-88.
6. Park S, Thakkar KN. "Splitting of the mind" revisited: recent neuroimaging evidence for functional dysconnection in schizophrenia and its relation to symptoms. The American journal of psychiatry. 2010;167(4):366-8.
7. Friston KJ, Frith CD. Schizophrenia: a disconnection syndrome? Clinical neuroscience. 1995;3(2):89-97.
8. Shenton ME, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. Schizophr Res. 2001;49(1-2):1-52.
9. Stephan KE, Baldeweg T, Friston KJ. Synaptic plasticity and dysconnection in schizophrenia. Biol Psychiatry. 2006;59(10):929-39.
10. Dolan RJ. Emotion, cognition, and behavior. Science. 2002;298(5596):1191-4.
11. Phelps EA. Emotion and cognition: insights from studies of the human amygdala. Annual review of psychology. 2006;57:27-53.
12. Velakoulis D, Wood SJ, Smith DJ, Soulsby B, Brewer W, Leeton L, et al. Increased duration of illness is associated with reduced volume in right medial temporal/anterior cingulate grey matter in patients with chronic schizophrenia. Schizophr Res. 2002;57(1):43-9.
13. Green MJ, Phillips ML. Social threat perception and the evolution of paranoia. Neurosci Biobehav Rev. 2004;28(3):333-42.

14. Herbener ES. Emotional memory in schizophrenia. Schizophr Bull. 2008;34(5):875-87.

15. Satterthwaite TD, Wolf DH, Loughead J, Ruparel K, Valdez JN, Siegel SJ, et al. Association of enhanced limbic response to threat with decreased cortical facial recognition memory response in schizophrenia. The American journal of psychiatry. 2010;167(4):418-26.

16. Walker EF, Diforio D. Schizophrenia: a neural diathesis-stress model. Psychological review. 1997;104(4):667-85.

17. Nekovarova T, Fajnerova I, Horacek J, Spaniel F. Bridging disparate symptoms of schizophrenia: a triple network dysfunction theory. Front Behav Neurosci. 2014;8:171.

18. Klein SB, Loftus J, Kihlstrom JF. Memory and temporal experience: the effects of episodic memory loss on an amnesic patient's ability to remember the past and imagine the future. . Soc Cogn. 2002;20:353-79.

19. Williams JM, Ellis NC, Tyers C, Healy H, Rose G, MacLeod AK. The specificity of autobiographical memory and imageability of the future. Memory & cognition. 1996;24(1):116-25.

20. D'Argembeau A, Raffard S, Van der Linden M. Remembering the past and imagining the future in schizophrenia. Journal of abnormal psychology. 2008;117(1):247-51.

21. Corlett PR, Simons JS, Pigott JS, Gardner JM, Murray GK, Krystal JH, et al. Illusions and delusions: relating experimentally-induced false memories to anomalous experiences and ideas. Front Behav Neurosci. 2009;3:53.

22. Corlett PR, Murray GK, Honey GD, Aitken MR, Shanks DR, Robbins TW, et al. Disrupted prediction-error signal in psychosis: evidence for an associative account of delusions. Brain. 2007;130(Pt 9):2387-400.

23. Callicott JH, Mattay VS, Verchinski BA, Marenco S, Egan MF, Weinberger DR. Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. The American journal of psychiatry. 2003;160(12):2209-15.

24. Johnston PJ, Katsikitis M, Carr VJ. A generalised deficit can account for problems in facial emotion recognition in schizophrenia. Biological psychology. 2001;58(3):203-27.

25. Kosaka H, Omori M, Murata T, Iidaka T, Yamada H, Okada T, et al. Differential amygdala response during facial recognition in patients with schizophrenia: an fMRI study. Schizophr Res. 2002;57(1):87-95.

26. Cannon TD, Glahn DC, Kim J, Van Erp TG, Karlsgodt K, Cohen MS, et al. Dorsolateral prefrontal cortex activity during maintenance and manipulation of information in working memory in patients with schizophrenia. Arch Gen Psychiatry. 2005;62(10):1071-80.

27. Ongur D, Cullen TJ, Wolf DH, Rohan M, Barreira P, Zalesak M, et al. The neural basis of relational memory deficits in schizophrenia. Arch Gen Psychiatry. 2006;63(4):356-65.

28. Rasetti R, Mattay VS, White MG, Sambataro F, Podell JE, Zoltick B, et al. Altered hippocampal-parahippocampal function during stimulus encoding: a potential indicator of genetic liability for schizophrenia. JAMA psychiatry. 2014;71(3):236-47.

29. Kaller CP, Loosli SV, Rahm B, Gossel A, Schieting S, Hornig T, et al. Working memory in schizophrenia: behavioral and neural evidence for reduced susceptibility to item-specific proactive interference. Biol Psychiatry. 2014;76(6):486-94.

30. Nejad AB, Madsen KH, Ebdrup BH, Siebner HR, Rasmussen H, Aggernaes B, et al. Neural markers of negative symptom outcomes in distributed working memory brain activity of antipsychotic-naive schizophrenia patients. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum. 2013;16(6):1195-204.

31. Wolf DH, Gur RC, Valdez JN, Loughead J, Elliott MA, Gur RE, et al. Alterations of fronto-temporal connectivity during word encoding in schizophrenia. Psychiatry research. 2007;154(3):221-32.

32. Sergerie K, Armony JL, Menear M, Sutton H, Lepage M. Influence of emotional expression on memory recognition bias in schizophrenia as revealed by fMRI. Schizophr Bull. 2010;36(4):800-10.

33. Wolf C, Linden S, Jackson MC, Healy D, Baird A, Linden DE, et al. Brain activity supporting working memory accuracy in patients with paranoid schizophrenia: a functional magnetic resonance imaging study. Neuropsychobiology. 2011;64(2):93-101.

34. Sapara A, Ffytche DH, Birchwood M, Cooke MA, Fannon D, Williams SC, et al. Preservation and compensation: the functional neuroanatomy of insight and working memory in schizophrenia. Schizophr Res. 2014;152(1):201-9.

35. Eich TS, Nee DE, Insel C, Malapani C, Smith EE. Neural correlates of impaired cognitive control over working memory in schizophrenia. Biol Psychiatry. 2014;76(2):146-53.

36. Weiss AP, Dewitt I, Goff D, Ditman T, Heckers S. Anterior and posterior hippocampal volumes in schizophrenia. Schizophr Res. 2005;73(1):103-12.

37. Wright IC, Rabe-Hesketh S, Woodruff PW, David AS, Murray RM, Bullmore ET. Meta-analysis of regional brain volumes in schizophrenia. The American journal of psychiatry. 2000;157(1):16-25.

38. Nelson MD, Saykin AJ, Flashman LA, Riordan HJ. Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging: a meta-analytic study. Arch Gen Psychiatry. 1998;55(5):433-40.

39. Wheeler AL, Chakravarty MM, Lerch JP, Pipitone J, Daskalakis ZJ, Rajji TK, et al. Disrupted prefrontal interhemispheric structural coupling in schizophrenia related to working memory performance. Schizophr Bull. 2014;40(4):914-24.

40. Wheeler AL, Voineskos AN. A review of structural neuroimaging in schizophrenia: from connectivity to connectomics. Frontiers in human neuroscience. 2014;8:653.

41. Kosaka H, Omori M, Murata T, Iidaka T, Yamada H, Okada T, et al. Differential amygdala response during facial recognition in patients with schizophrenia: an fMRI study. Schizophr Res. 2002;57(1):87-95.

42. Volk DW, Lewis DA. Early developmental disturbances of cortical inhibitory neurons: contribution to cognitive deficits in schizophrenia. Schizophr Bull. 2014;40(5):952-7.

43. Ruggiero G, Sergi I, Iachini T. Gender differences in remembering and inferring spatial distances. Memory. 2008;16(8):821-35.

44. Linn MC, Petersen AC. Emergence and characterization of sex differences in spatial ability: a meta-analysis. Child Dev. 1985;56(6):1479-98.

45. Voyer D, Voyer S, Bryden MP. Magnitude of sex differences in spatial abilities: a meta-analysis and consideration of critical variables. Psychol Bull. 1995;117(2):250-70.

46. Halari R, Sharma T, Hines M, Andrew C, Simmons A, Kumari V. Comparable fMRI activity with differential behavioural performance on mental rotation and overt verbal fluency tasks in healthy men and women. Exp Brain Res. 2006;169(1):1-14.

47. Viveros MP, Mendrek A, Paus T, Lopez-Rodriguez AB, Marco EM, Yehuda R, et al. A comparative, developmental, and clinical perspective of neurobehavioral sexual dimorphisms. Front Neurosci. 2012;6:84.

48. Goldstein JM, Seidman LJ, Goodman JM, Koren D, Lee H, Weintraub S, et al. Are there sex differences in neuropsychological functions among patients with schizophrenia? The American journal of psychiatry. 1998;155(10):1358-64.

49. Vaskinn A, Sundet K, Simonsen C, Hellvin T, Melle I, Andreassen OA. Sex differences in neuropsychological performance and social functioning in schizophrenia and bipolar disorder. Neuropsychology. 2011;25(4):499-510.

50. Voglmaier MM, Seidman LJ, Niznikiewicz MA, Dickey CC, Shenton ME, McCarley RW. A comparative profile analysis of neuropsychological function in men and women with schizotypal personality disorder. Schizophr Res. 2005;74(1):43-9.

51. Torniainen M, Suvisaari J, Partonen T, Castaneda AE, Kuha A, Perala J, et al. Sex differences in cognition among persons with schizophrenia and healthy first-degree relatives. Psychiatry research. 2011;188(1):7-12.

52. Han M, Huang XF, Chen da C, Xiu MH, Hui L, Liu H, et al. Gender differences in cognitive function of patients with chronic schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2012;39(2):358-63.

53. Zhang XY, Chen da C, Xiu MH, Yang FD, Haile CN, Kosten TA, et al. Gender differences in never-medicated first-episode schizophrenia and medicated chronic schizophrenia patients. The Journal of clinical psychiatry. 2012;73(7):1025-33.

54. Brebion G, Villalta-Gil V, Autonell J, Cervilla J, Dolz M, Foix A, et al. Cognitive correlates of verbal memory and verbal fluency in schizophrenia, and differential effects of various clinical symptoms between male and female patients. Schizophr Res. 2013;147(1):81-5.

55. Han M, Huang XF, Chen DC, Xiu MH, Hui L, Liu H, et al. Gender differences in cognitive function of patients with chronic schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2012;39(2):358-63.

56. Lakis N. An fMRI study of emotional episodic memory in schizophrenia: Effects of diagnosis and sex. Montreal, Quebec, Canada: University of Montreal; 2012.

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

58. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. 1971;9(1):97-113.

59. Spitzer RL, Williams JB, Gibbon M, First MB. The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. Arch Gen Psychiatry. 1992;49(8):624-9.

60. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261-76.

61. Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry. 2003;64(6):663-7.

62. Lang PJ, Bradley MM, Cuthbert BN. International Affective Picture System (IAPS): Technical Manual and Affective. . Gainesville, FL: NIMH Center for the Study of Emotion and Attention, University of Florida.; 1997.

63. Lakis N, Jimenez JA, Mancini-Marie A, Stip E, Lavoie ME, Mendrek A. Neural correlates of emotional recognition memory in schizophrenia: effects of valence and arousal. Psychiatry research. 2011;194(3):245-56.

64. Bourque J, Mendrek A, Durand M, Lakis N, Lipp O, Stip E, et al. Cannabis abuse is associated with better emotional memory in schizophrenia: a functional magnetic resonance imaging study. Psychiatry research. 2013;214(1):24-32.

65. Lakis N, Mendrek A. Individuals diagnosed with schizophrenia assign emotional importance to neutral stimuli: an FMRI study. ISRN Psychiatry. 2013;2013:965428.

66. Ashburner J. A fast diffeomorphic image registration algorithm. Neuroimage. 2007;38(1):95-113.

67. Ashburner J, Friston KJ. Computing average shaped tissue probability templates. Neuroimage. 2009;45(2):333-41.

68. Ashburner J, Friston KJ. Why voxel-based morphometry should be used. Neuroimage. 2001;14(6):1238-43.

69. Stegmayer K, Horn H, Federspiel A, Razavi N, Bracht T, Laimbock K, et al. Ventral striatum gray matter density reduction in patients with schizophrenia and psychotic emotional dysregulation. Neuroimage Clin. 2014;4:232-9.

70. Stepens A, Stagg CJ, Platkajis A, Boudrias MH, Johansen-Berg H, Donaghy M. White matter abnormalities in methcathinone abusers with an extrapyramidal syndrome. Brain. 2010;133(Pt 12):3676-84.

71. Hugdahl K, Loberg EM, Nygard M. Left temporal lobe structural and functional abnormality underlying auditory hallucinations in schizophrenia. Front Neurosci. 2009;3(1):34-45.

72. Andreasen NC, Pierson R. The role of the cerebellum in schizophrenia. Biol Psychiatry. 2008;64(2):81-8.

73. Yun JY, Hur JW, Jung WH, Jang JH, Youn T, Kang DH, et al. Dysfunctional role of parietal lobe during self-face recognition in schizophrenia. Schizophr Res. 2014;152(1):81-8.

74. Gur RE, Cowell PE, Latshaw A, Turetsky BI, Grossman RI, Arnold SE, et al. Reduced dorsal and orbital prefrontal gray matter volumes in schizophrenia. Arch Gen Psychiatry. 2000;57(8):761-8.

75. Li M, Chen Z, Deng W, He Z, Wang Q, Jiang L, et al. Volume increases in putamen associated with positive symptom reduction in previously drug-naive schizophrenia after 6 weeks antipsychotic treatment. Psychol Med. 2012;42(7):1475-83.

76. Ebdrup BH, Glenthoj B, Rasmussen H, Aggernaes B, Langkilde AR, Paulson OB, et al. Hippocampal and caudate volume reductions in antipsychotic-naive first-episode schizophrenia. J Psychiatry Neurosci. 2010;35(2):95-104.

77. Cabeza R, Ciaramelli E, Olson IR, Moscovitch M. The parietal cortex and episodic memory: an attentional account. Nature reviews Neuroscience. 2008;9(8):613-25.

78. Niznikiewicz M, Donnino R, McCarley RW, Nestor PG, Iosifescu DV, O'Donnell B, et al. Abnormal angular gyrus asymmetry in schizophrenia. The American journal of psychiatry. 2000;157(3):428-37.

79. Wolf RC, Hose A, Frasch K, Walter H, Vasic N. Volumetric abnormalities associated with cognitive deficits in patients with schizophrenia. Eur Psychiatry. 2008;23(8):541-8.

80. Lepage M, Pelletier M, Achim A, Montoya A, Menear M, Lal S. Parietal cortex and episodic memory retrieval in schizophrenia. Psychiatry research. 2010;182(3):191-9.

81. Barch DM, Csernansky JG. Abnormal parietal cortex activation during working memory in schizophrenia: verbal phonological coding disturbances versus domain-general executive dysfunction. The American journal of psychiatry. 2007;164(7):1090-8.

82. Binder JR, Desai RH, Graves WW, Conant LL. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cerebral cortex. 2009;19(12):2767-96.

83. Chambers CD, Payne JM, Stokes MG, Mattingley JB. Fast and slow parietal pathways mediate spatial attention. Nature neuroscience. 2004;7(3):217-8.

84. Pearlson GD, Petty RG, Ross CA, Tien AY. Schizophrenia: a disease of heteromodal association cortex? Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 1996;14(1):1-17.

85. Rametti G, Segarra N, Junque C, Bargallo N, Caldu X, Ibarretxe N, et al. Left posterior hippocampal density reduction using VBM and stereological MRI procedures in schizophrenia. Schizophr Res. 2007;96(1-3):62-71.

86. Suazo V, Diez A, Montes C, Molina V. Structural correlates of cognitive deficit and elevated gamma noise power in schizophrenia. Psychiatry Clin Neurosci. 2014;68(3):206-15.

87. Crossley NA, Mechelli A, Scott J, Carletti F, Fox PT, McGuire P, et al. The hubs of the human connectome are generally implicated in the anatomy of brain disorders. Brain. 2014;137(Pt 8):2382-95.

88. Ellison-Wright I, Bullmore E. Meta-analysis of diffusion tensor imaging studies in schizophrenia. Schizophr Res. 2009;108(1-3):3-10.

89. Ellison-Wright I, Bullmore E. Anatomy of bipolar disorder and schizophrenia: a meta-analysis. Schizophr Res. 2010;117(1):1-12.

90. Ross CA, Pearlson GD. Schizophrenia, the heteromodal association neocortex and development: potential for a neurogenetic approach. Trends in neurosciences. 1996;19(5):171-6.

91. Alexander-Bloch AF, Vertes PE, Stidd R, Lalonde F, Clasen L, Rapoport J, et al. The anatomical distance of functional connections predicts brain network topology in health and schizophrenia. Cerebral cortex. 2013;23(1):127-38.

92. Honey CJ, Sporns O, Cammoun L, Gigandet X, Thiran JP, Meuli R, et al. Predicting human resting-state functional connectivity from structural connectivity. Proceedings of the National Academy of Sciences of the United States of America. 2009;106(6):2035-40.

93. Skelley SL, Goldberg TE, Egan MF, Weinberger DR, Gold JM. Verbal and visual memory: characterizing the clinical and intermediate phenotype in schizophrenia. Schizophr Res. 2008;105(1-3):78-85.

94. Jimenez J, Mancini-Marie A, Mendrek A. The case for not combining men and women in neurocognitive studies for schizophrenia. Schizophr Res. 2009;108(1-3):293-4.

95. Jimenez JA, Mancini-Marie A, Lakis N, Rinaldi M, Mendrek A. Disturbed sexual dimorphism of brain activation during mental rotation in schizophrenia. Schizophr Res. 2010;122(1-3):53-62.

96. Gur RC, Alsop D, Glahn D, Petty R, Swanson CL, Maldjian JA, et al. An fMRI study of sex differences in regional activation to a verbal and a spatial task. Brain and language. 2000;74(2):157-70.

97. Astor RS, Ortiz, M.L., Sutherland, R.J. . A characterization of performance by men and women in a virtual Morris water task: A large and reliable sex difference. Behavioural Brain Research. 1998 93 185-90.

98. Mendrek A, Stip E. Sexual dimorphism in schizophrenia: is there a need for gender-based protocols? Expert Rev Neurother. 2011;11(7):951-9.

99. Mendrek A. [Sexual dismorphism in schizophrenia]. Sante mentale au Quebec. 2007;32(1):351-65.

100. Mendrek A. Reversal of normal cerebral sexual dimorphism in schizophrenia: evidence and speculations. Medical hypotheses. 2007;69(4):896-902.

101. Cohen AS, Minor KS. Emotional experience in patients with schizophrenia revisited: meta-analysis of laboratory studies. Schizophr Bull. 2010;36(1):143-50.

102. Herbener ES, Rosen C, Khine T, Sweeney JA. Failure of positive but not negative emotional valence to enhance memory in schizophrenia. Journal of abnormal psychology. 2007;116(1):43-55.

103. Myin-Germeys I, Nicolson NA, Delespaul PA. The context of delusional experiences in the daily life of patients with schizophrenia. Psychol Med. 2001;31(3):489-98.

104. Phillips LJ, Francey SM, Edwards J, McMurray N. Strategies used by psychotic individuals to cope with life stress and symptoms of illness: a systematic review. Anxiety, stress, and coping. 2009;22(4):371-410.

105. Matud MP. Gender differences in stress and coping styles. Personality and Individual Differences. 2004;37:1401-15.

106. Brougham RR, Zail, C. M., Mendoza, C. M., Miller, J. R. . Stress, sex differences, and coping strategies among college students. Current Psychology 2009;28:85-97.

107. Highley JR, DeLisi LE, Roberts N, Webb JA, Relja M, Razi K, et al. Sex-dependent effects of schizophrenia: an MRI study of gyral folding, and cortical and white matter volume. Psychiatry research. 2003;124(1):11-23.

108. Wang L, Li Y, Metzak P, He Y, Woodward TS. Age-related changes in topological patterns of large-scale brain functional networks during memory encoding and recognition. Neuroimage. 2010;50(3):862-72.

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Figure and table legends:

Table 1. Clinical assessments in schizophrenia patients

Table 2. ANOVA results displaying regions of GMD and WMD differences between the SZ and NC with memory accuracy in voxel-based morphometry. The values given are the stereotactic (MNI) coordinates and the T values of each anatomical region. SPM maps were thresholded at $p < 0.05$ (corrected, voxel-level); minimum cluster size threshold of 100 voxels.

Table 3. Regional GMD and WMD differences between the SZ and NC associated with memory accuracy

Table 4. Post hoc multiple comparison show sex differences in performance in the three condition: positive, negative and neutral condition.

Figure 1. Figure presenting GMD correlating with PMA, NMA and ZMA.

Figure 2. Figure presenting WMD correlating with PMA, NMA and ZMA

Figure 3. Boxplot representing mean GMD and WMD values between SZ and NC. Note the variation between GMD and WMD in NC. When we consider the variation between GMD and WMD we note that it is relatively diminished in the SZ.

Figure 4. Bar graphic representing the mean PMA, NMA and ZMA between NC and SZ (bars represent error bars with a $p<0.05$).

Figure 5. Scatter plot representing regression analyses between GMD, WMD and behavioral memory accuracy scores. Note that NC are clustered together with no visually noted variability. We note that SZ are disordered reflecting the schizophrenia disorder heterogeneity and variability within subjects. The plots show the curvilinear (quadratic) relationships between GMD and WMD respectively and memory accuracy scores. Both the linear and quadratic effects are significant.

Figure 6. Scatter plot showing total WMD inversely correlating with NMA and PMA only in SZ-M. GMD were positively correlated with NMA in only NC-M.

Table 1. Clinical assessments in schizophrenia patients

	SZ-M Mean (SD)	SZ-F 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
PANSS positive	17.95 (5.33)	19.65 (8.03)	0.435
PANSS negative	19.50 (5.36)	21.25 (8.30)	0.434
PANSS general	38.75 (5.27)	43.10 (12.92)	0.171
Chlorpromazine equivalence	722.50 (383.74)	443.33 (280.94)	0.012
Age of onset	19.89 (2.97)	24.40 (7.75)	0.007
Duration of illness	11.57 (7.74)	8.25 (5.7)	0.136
Parental socioeducational status	2.82 (.612)	2.62 (1.06)	0.470

Table 2. Cognitive behavioral assessments in schizophrenia patients and normal controls

df=77

	NC-M		SZ-M		p	NC-F		SZ-F		p	F
	Mean	**SD**	**Mean**	**SD**		**Mean**	**SD**	**Mean**	**SD**		
Block design from WAIS-III	12.86	2.851	8.79	2.820	0.001	10.69	3.615	9.53	3.681	0.410	6.096
Similitudes from WAIS-III	11.67	3.022	7.05	2.392	0.001	10.93	2.052	7.50	2.229	0.001	16.721
Vocabulary from WAIS-III	11.05	2.312	6.16	2.672	0.001	9.46	1.854	6.32	2.311	0.001	20.527
Raven percentile	78.24	19.98	42.18	22.54	0.001	83.80	15.79	60.28	24.27	0.003	14.451

df=77

Table 3. Regional gray and white matter density differences between the schizophrenia group and normal controls associated with memory accuracy

	Brain region, K (voxels), t ($p<0.05$ $P_{FWE-corr}$) MNI coordinates	Brain region, K (voxels), t ($p<0.05$ $P_{FWE-corr}$) MNI coordinates	Brain region, K (voxels), t ($p<0.05$ $P_{FWE-corr}$) MNI coordinates
	Negative IAPS images	Positive IAPS images	Neutral IAPS images
GMD NC > SZ	Posterior parietal cortex (k=486), (t=4.24), (-45, -19, 27) Lentiform/putamen/caudate (k=819), (t=4.01), (18, 6, 13 and 12, 3 53) Inferior frontal/orbital cortex (k=236), (t=3.86), (-39, 18, -6)	Temporal lobe, fusiform gyrus (k=153), (t=3.63), (-34, -36, -9)	Cerebellum anterior lobe (k=174), (t=4.21), (-50, -49, -27)
GMD SZ > NC	Inferior occipital cortex (k=100), (t=4.48), (-27, -87, -9)	-	-
WMD NC > SZ	Postcentral parietal cortex (k=288), (t=4.57), (-63, -16, 28)	Inferior temporal (k=156), (t=4.24), (-50, -18, -15) Precuneus parietal (k=106), (t=4.13), (-42, -60, 31) Frontal lobe (k=159), (t=3.76), (-12, 24, 1)	Middle temporal (k=297), (t=3.27) (-54, -6, -6)
WMD SZ > NC	Lingual occipital (k=352), (4.51), (-36, -88, -4)	Angular parietal (k=261), (t=4.10), (-42, -60, 31)	Superior temporal (k=153), (t=3.54), (53, -42, 15)

Table 4. Memory accuracy performance between groups (Post hoc multiple comparison - ANOVA)

	NC-M		SZ-M		p	NC-F		SZ-F		p	F
Condition	**Mean**	**SD**	**Mean**	**SD**	**df=77**	**Mean**	**SD**	**Mean**	**SD**	**df=77**	
NMA	0.84	0.18	0.61	0.22	0.003	0.83	0.10	0.65	0.28	0.02	7.473
PMA	0.85	0.15	0.59	0.23	0.001	0.84	0.11	0.57	0.29	0.001	12.291
ZMA	0.79	0.15	0.50	0.21	0.001	0.75	0.13	0.52	0.23	0.001	14.189

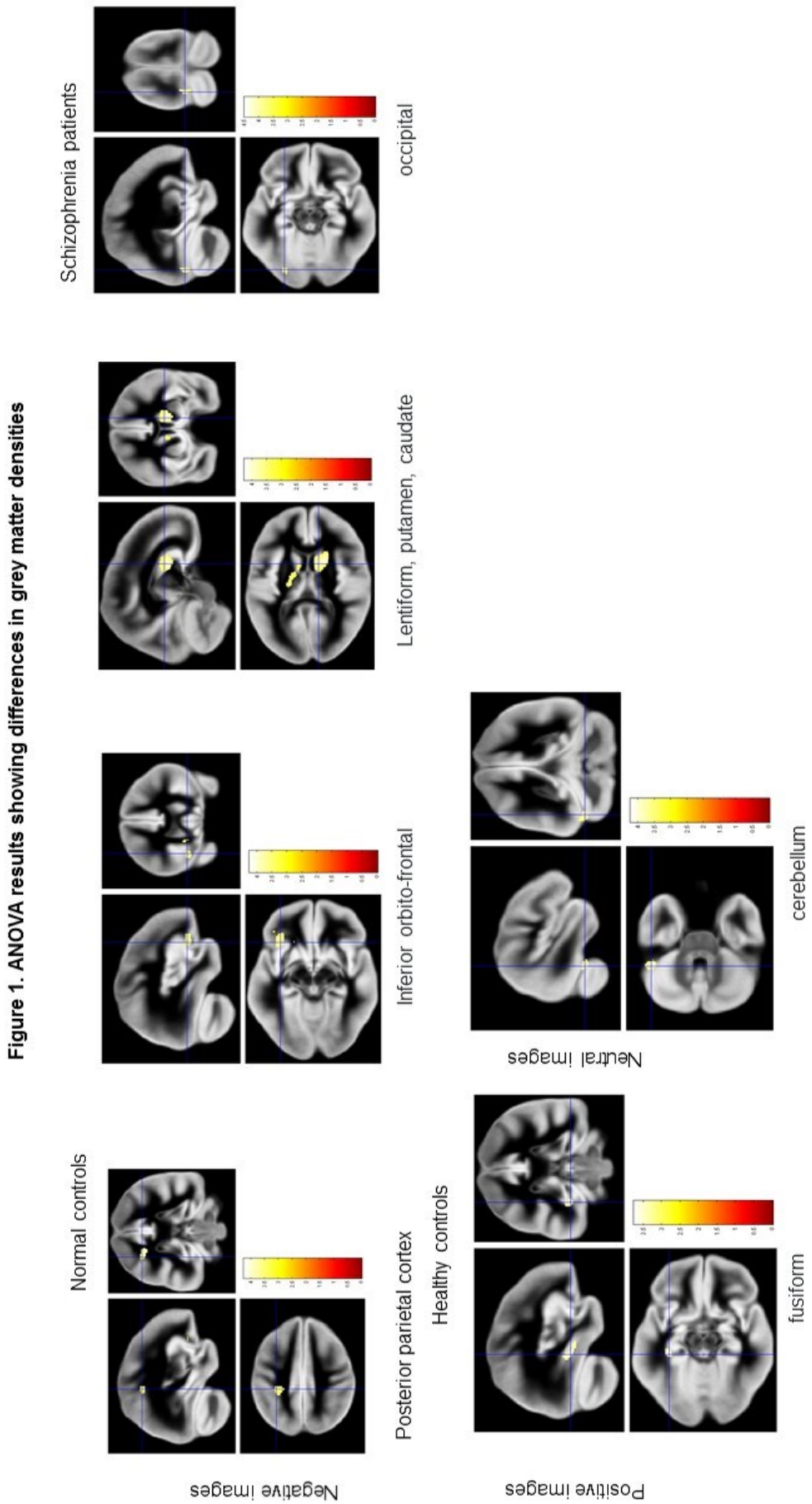

Figure 1. ANOVA results showing differences in grey matter densities

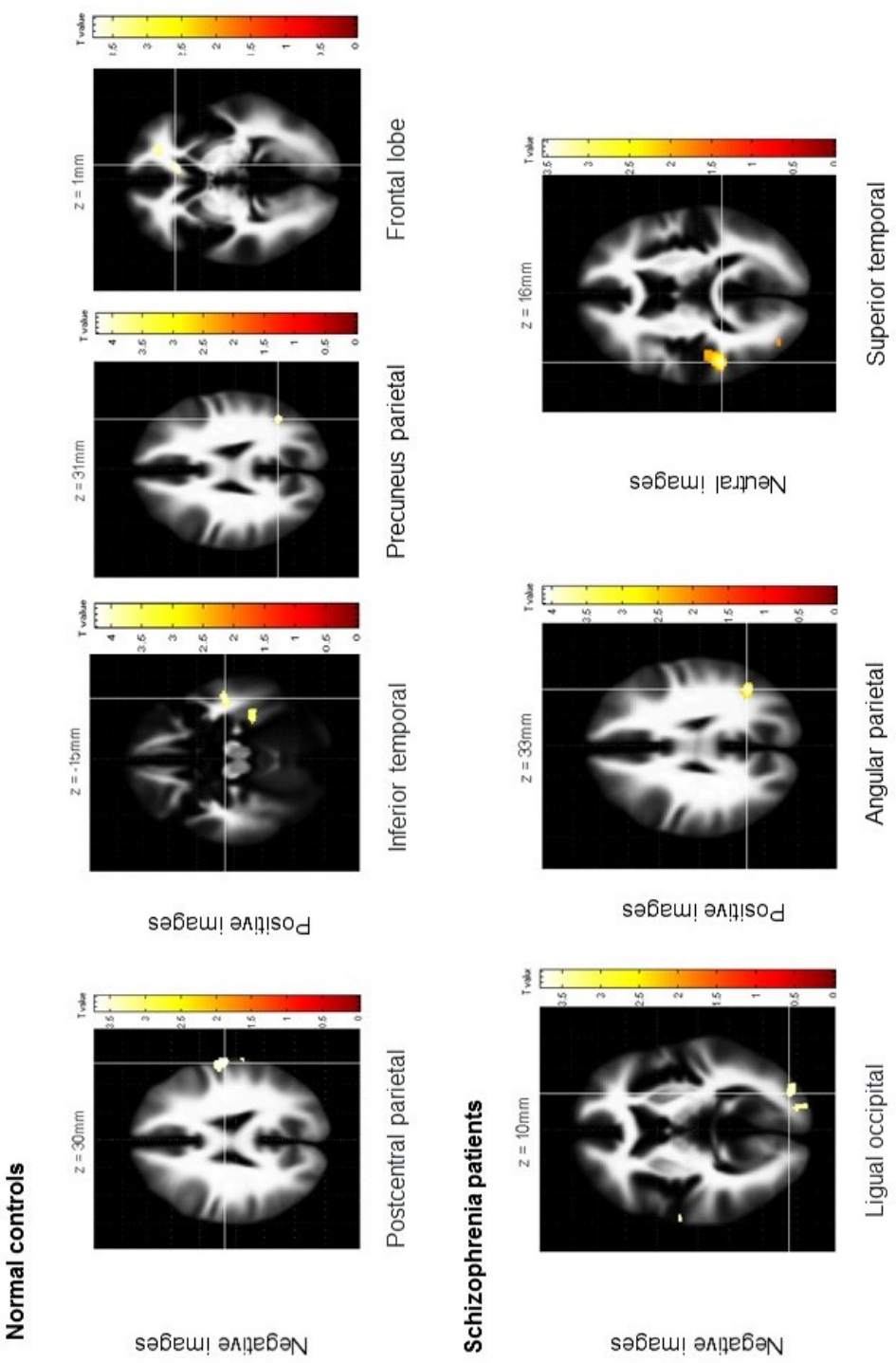

Figure 2. ANOVA results showing differences in white matter densities

Figure 3. Boxplot representing mean GMD and WMD between schizophrenia patients and normal controls

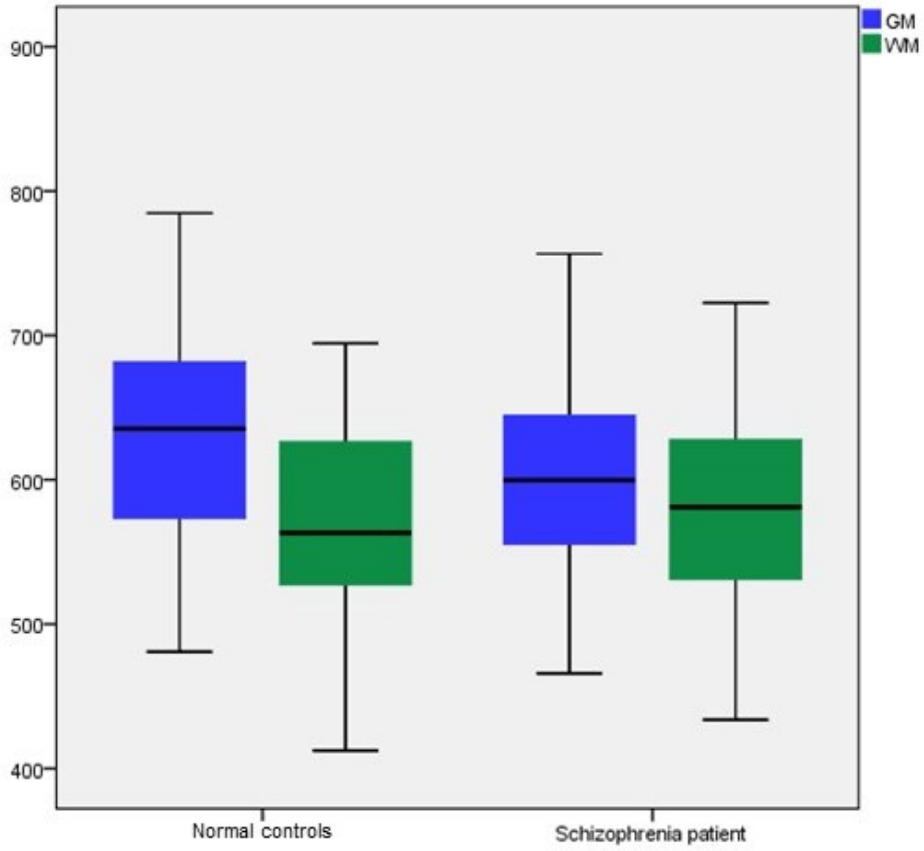

Figure 4. Mean behavioral accuracy recall in schizophrenia patients and normal controls

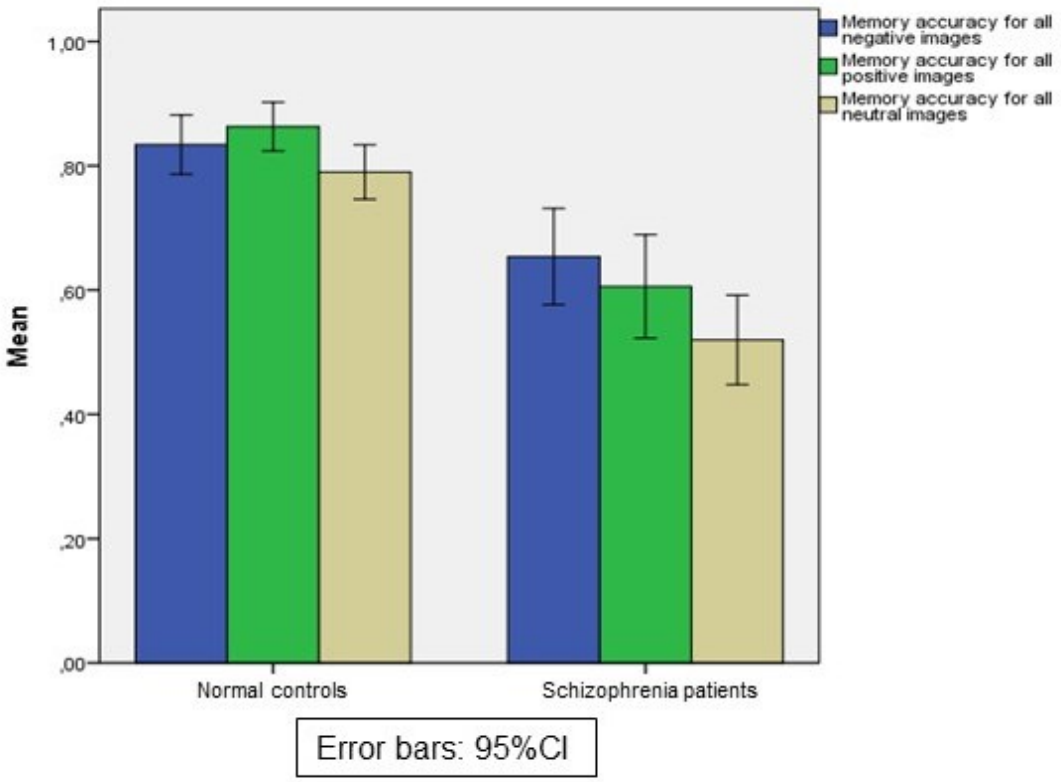

Figure 5. Scatter plot representing regression analyses between GMD, WMD and behavioral memory accuracy scores in schizophrenia patients and normal controls

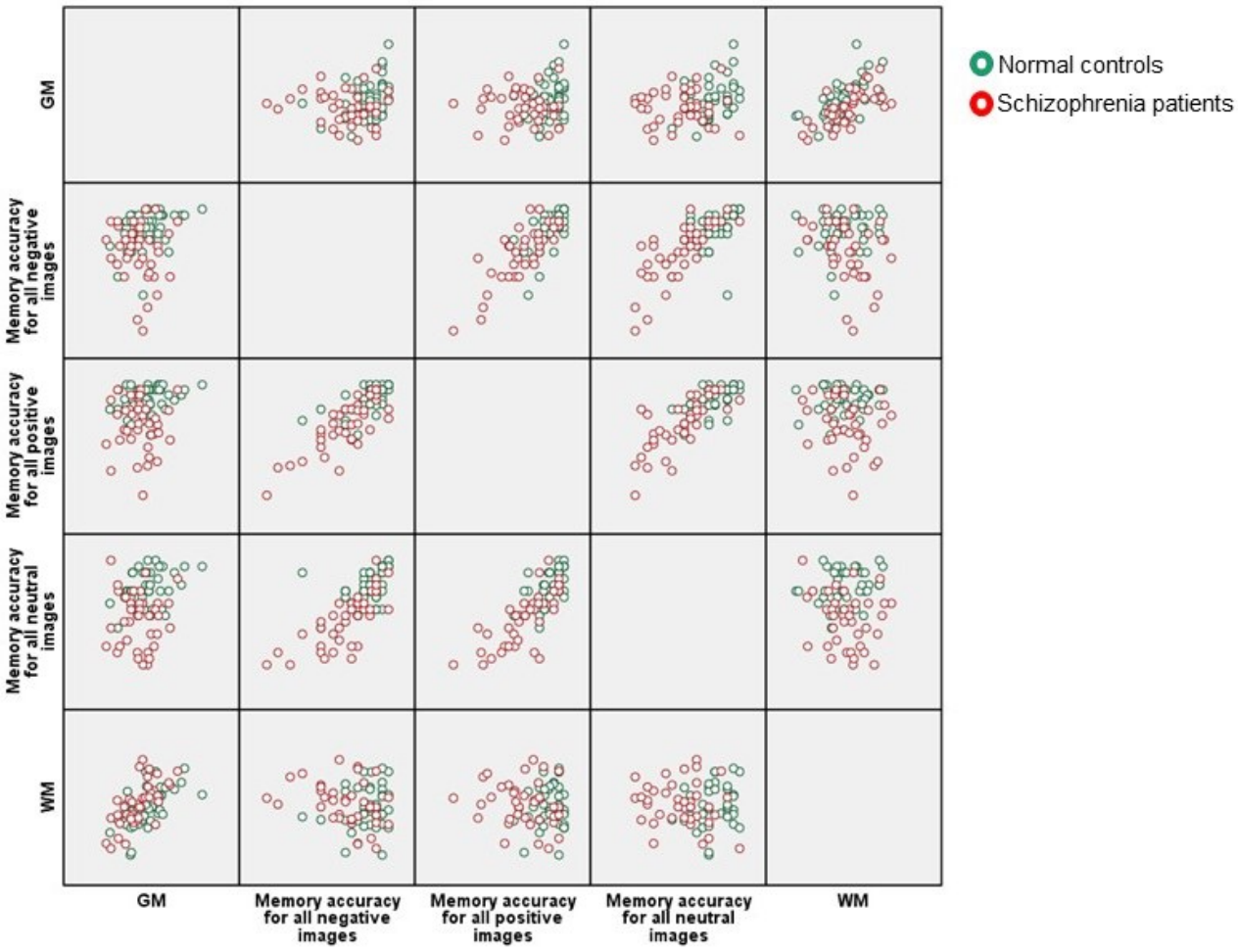

Figure 6. Result of regression analyses between grey and white matter densities with symptoms in male groups

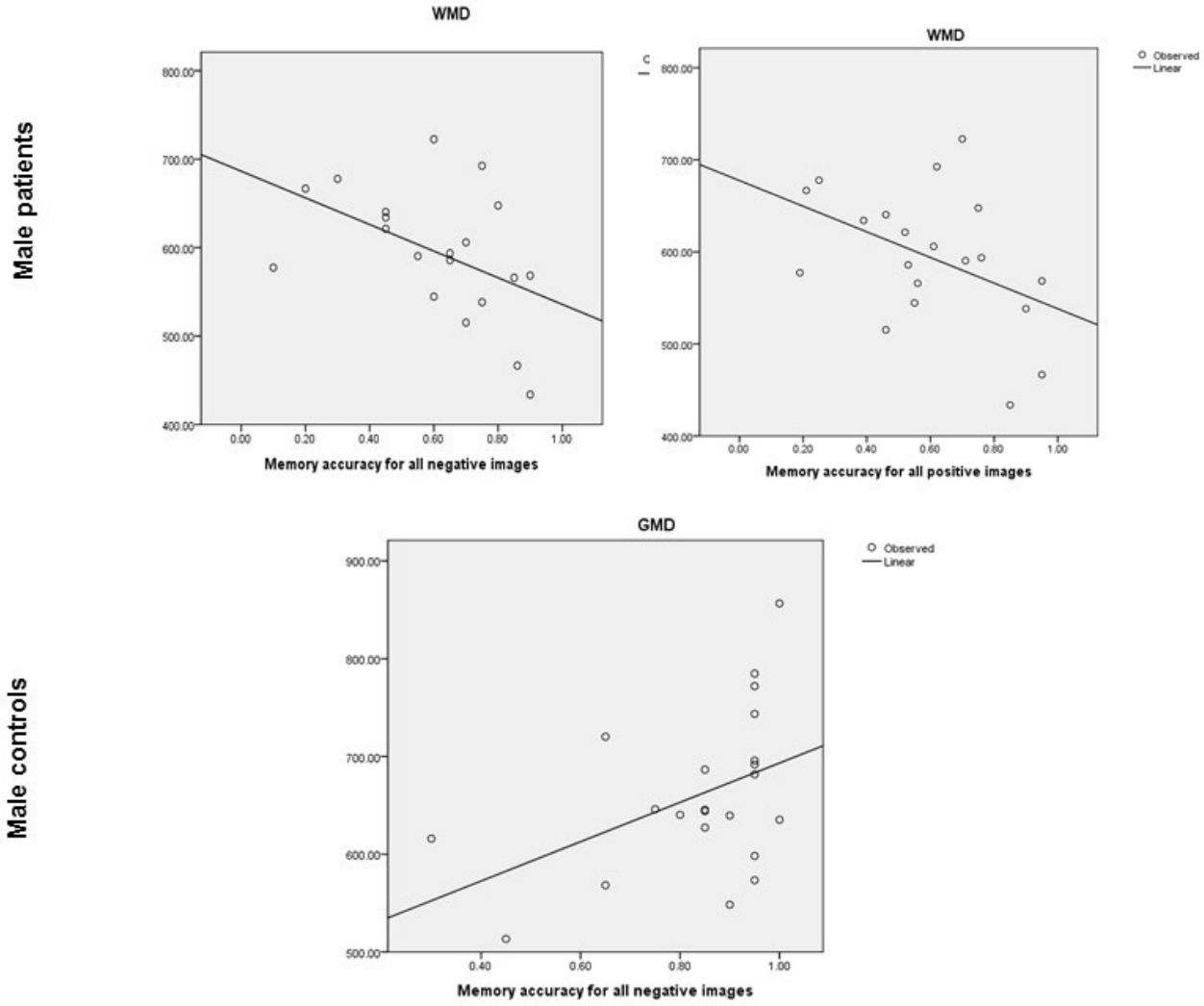

Figure and table legends:

Table 2. ANOVA results displaying regions of GMD and WMD differences between the SZ and NC with memory accuracy using voxel-based morphometry. The values given are the stereotactic (MNI) coordinates and the T values of each anatomical region. SPM maps were thresholded at $p < 0.05$ (corrected, voxel-level); minimum cluster size threshold of 100 voxels, df=77.

Legend Figure 3. Boxplot representing mean GMD and WMD values between SZ and NC. Note the variation between GMD and WMD in NC. When we consider the variation between GMD and WMD we note that it is relatively diminished in the SZ.

Legend Figure 4. Bar graphic representing the mean behavioral accuracy recall of negative, positive and neutral IAPS images between NC and SZ (bars represent error bars with a $p<0.05$).

Legend Figure 5. Scatter plot representing regression analyses between GMD, WMD and behavioral memory accuracy scores. Note that NC are clustered together with no visually noted variability. We note that SZ are disordered reflecting the schizophrenia disorder heterogeneity and variability within subjects. The plots show the curvilinear (quadratic) relationships between GMD and WMD respectively and memory accuracy scores. Both the linear and quadratic effects are significant.

8 Discussion

We hypothesized that schizophrenia patients would exhibit sex-dependent abnormalities in their brain morphology, and that these abnormalities would be related to main aspects of the disorder, including symptoms, cognition, and emotion. To test these hypotheses, we measured cortical gyrification and its relationship with schizophrenia symptoms, we examined gray and white matter densities and their relationship with symptoms, and lastly we investigated grey and white matter densities and their relationship with cognitive performance. In addition to testing these hypotheses, a complete review of the literature was undertaken. Findings related to schizophrenia in general were presented, and revealed some inconsistencies in results. A specific review of the literature in relation to sex differences in schizophrenia concluded that differences between males and females are present in almost all aspects of the disorder, including incidence, prevalence, risk, age of onset, premorbid deficits, course of the illness and prognosis, comorbidities, psychosocial functioning and adjustment, clinical expression, severity of symptoms, resilience to the disorder, cognitive and emotional deficits, treatment response, medication efficacy and side effects, cortical and subcortical brain morphology. Our literature review demonstrates that all these aspects seem to be more severe in male patients with schizophrenia.

This work presented in the first paper is considered one of the first to investigate sex differences using gyrification index. Firstly, using cortical thickness measurements we investigated differences in GI between schizophrenia patients and control participants, as well as sex-specific differences. Secondly, we correlated cortical gyrification findings with schizophrenia symptoms and probed if sex differences were present in these associations. This work is, to the best of our knowledge, the first report of sex differences interacting with the duration of illness. Another important and unanticipated finding was that very few correlations were found between GI abnormalities and symptoms in the schizophrenia group as a whole and when analyzed separately sexing males and females. In addition, abnormalities in gyrification index in our group of schizophrenia patients in comparison to healthy controls, were not the same regions that correlated with schizophrenia clinical symptoms as measured by the PANSS. These intriguing findings led to the work presented in the second paper. Here we postulated that deeper structures and white matter are associated with symptoms of schizophrenia, and that this relation differs in male and female patients. We used voxel-based morphometry to investigate deeper structures and white matter

densities. Of particular interest is the association between greater WMD and more severe symptom scores of conceptual disorganization and attention deficits. In terms of correlations, while females revealed no specific correlation between total GMD, WMD, CSF, or total brain volume and schizophrenia symptoms, WMD in male patients correlated negatively with ideas of grandiosity, and positively with conceptual disorientation and attention deficits. To our knowledge, this is the first study to report a direct relationship between white matter density and these symptoms. This study demonstrated that even though gyrification measures were not markedly correlated with symptoms, differences in gray and white matter densities were. The third paper investigates another core aspect of schizophrenia: cognition and emotion. We investigated regional abnormalities in gray and white matter using VBM in relation to cognitive and emotional functioning -a sphere severely impaired in schizophrenia- and their relation to sex differences. Here, sex difference reappear significantly such that total white matter density in males with schizophrenia correlated negatively with memory accuracy of positive and negative images and no such associations were found in female patients.

8.1 Summary of main findings

Findings related to sex differences in schizophrenia:

Study 1.

1. SZ-M had significantly lower values of the GI in the right hemisphere in SZ-M relative to the same-sex controls (no difference between female groups).
2. GI values decrease with age in healthy controls (with no sex difference) and in patients (greater in SZ-M than SZ-F) with a more progressive deterioration in the right hemisphere in schizophrenia.
3. GI values decrease with the duration of illness in SZ-M but not in SZ-F.
4. SZ-M had a significantly higher GI relative to the same-sex controls in the right temporal lobe.
5. SZ-F had significant lower GI in left frontal, bilateral temporal and left parietal lobes relative to the same-sex controls.
6. Positive correlation between negative symptoms and the right occipital GI in patients regardless of sex.
7. SZ-M had an inverse correlation in the left occipital GI with negative symptoms.

8. SZ-F had positive correlations between negative symptoms and the right occipital GI.

Study 2.

9- SZ-M revealed decreased total GMD compared to NC-M.
10- No differences in GMD, WMD, CSF or total brain volume were observed in female groups.
11- SZ-F showed no correlations between total GMD, WMD, CSF, or total brain volume and schizophrenia symptoms.
12- SZ-M showed inverse correlation between WMD and ideas of grandiosity.
13- SZ-M showed correlations between WMD and disorientation.
14- SZ-M showed correlations between both GMD and WMD and attention deficits.

Study 3

15. NC-M significantly out-performed SZ-M on all subcategories of the WAIS-III and Raven percentile tests.
16. SZ-F when compare to NC-F showed fewer deficits than SZ-M: in the Raven percentile and only two categories of the WAIS-III (Similitudes from WAIS-III and Vocabulary from WAIS-III).
17. SZ-M showed inverse correlations between WMD and NMA and PMA.
18. NC-M, total GMD correlated with NMA; in female groups, no correlations were found.

<u>Findings related to differences between SZ and NC:</u>

Study 1.

1. Significantly lower values of the overall GI in SZ relative to NC.
2. SZ had lower GI in bilateral frontal, temporal and parietal lobes.

Study 2.

3. SZ had lower GMD in the anterior cingulate cortex, left middle temporal in comparison to NC.
4. SZ had higher GMD in the left posterior cingulate compared to NC.
5. SZ had lower WMD in the left inferior frontal rectal region and the left posterior parietal region in comparison to NC.

6. SZ showed correlations between positive symptoms and GMD in the left insula and right caudate.
7. SZ showed correlations between negative symptoms and GMD in the right middle frontal and the posterior lobe of right cerebellum (Uvula).
8. SZ showed inverse correlations between positive symptoms and GMD in the right parietal (precuneus), the posterior lobe of left cerebellum (Uvula).
9. SZ showed inverse correlations between negative symptoms and GMD in the anterior lobe of the left cerebellum.
10. SZ showed correlations between positive symptoms and WMD in the right middle frontal region.
11. SZ showed correlation between negative symptoms were and WMD in the right superior frontal region.
12. SZ showed inverse correlations between positive symptoms and WMD in both right inferior occipital and right occipital cuneus regions.
13. SZ showed inverse correlations between negative symptoms and WMD in the left superior frontal region.
14. SZ showed correlations between the conceptual disorganization symptom and both GMD and WMD.
15. SZ showed inverse correlations between GMD and lack of spontaneity and hallucinations.
16. SZ showed inverse correlations between WMD and hostility and grandiosity.

Study 3.

17. No significant difference was found between SZ and NC in total brain volume or total WMD. NC had higher GMD than SZ.
18. NC performed better that SZ on all memory accuracy tasks (NMA, PMA ZMA).
19. NC showed higher GMD correlation with NMA in the right posterior parietal cortex, lentiform, putamen, and caudate; the left inferior orbitofrontal cortex.
20. NC showed higher GMD correlation with ZMA in the left anterior cerebellum.
21. NC showed higher WMD correlation with NMA in the left postcentral parietal region.
22. NC showed higher WMD correlation with PMA in the left inferior temporal, left precuneus parietal, and left frontal regions.

23. NC showed higher WMD correlation with ZMA in the left middle temporal region for ZMA.
24. NC showed higher GMD correlation with PMA in the left temporal and fusiform region.
25. SZ showed higher GMD correlation with NMA in the left inferior occipital cortex.
26. SZ did not show any GMD correlation with PMA or ZMA.
27. SZ showed higher WMD correlation with NMA in left lingual occipital region.
28. SZ showed higher WMD correlation with PMA in the left angular parietal region.
29. SZ showed higher WMD correlation with NMA in the right superior temporal region.

Findings in schizophrenia patients

Structural findings:

The results obtained in our study were overall congruent with previous findings of decreased volume, density and cortical thickness in patients with schizophrenia relative to controls (191, 266-268, 271-275, 575). As reported in numerous other studies (270, 278, 576-580) our sample of schizophrenia patients had lower gray matter densities in the anterior cingulate cortex and left middle temporal gyrus in comparison with healthy controls. It is of particular interest that decreases in gray matter densities were not necessarily related to abnormalities in gyrification index in patients in our study. A recent study by Kong et al., (2014) similarly found discordance between gray matter volume and cortical thickness such that patients had reduced gray matter while cortical thickness remained relatively preserved. The authors suggested that differences between gray matter volume and thickness could be jointly driven by surface area, gray/white matter intensity contrast, and curvature (580). Consistently with our results, a review by Crossley and colleagues (2014) stated that lesions in schizophrenia were concentrated in both frontal and temporal cortical hubs (581).

In addition to frontal and temporal anomalies, patients had higher gray matter densities in the left posterior cingulate compared to healthy controls. This region seems to be more preserved in the early stages of illness and increased GMD may indicate a compensatory mechanism in response to the anterior cingulate deficits (18, 19).

Symptom related findings

The positive correlation between the PANSS positive and the caudate and insula in schizophrenia patients is intriguing. The caudate has been reportedly involved in the neurobiology of schizophrenia positive symptoms in relation to dopamine dysfunction (90, 91, 582), although caudate abnormalities may be related to medication exposure (583). The insula is involved in emotional interoceptive representations (584), and in acoustico-verbal hallucinations (585). 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-sensory processes, hence providing a hub that integrates salient stimuli with somatosensory and autonomic information (586-589). The increased GMD could be associated with the over stimulation of cognitive, emotional and somato-sensorial processes regulated by the insula resulting in symptoms such as delusions and hallucinations which are characterized by amplification of emotional and sensory motor perception and processing.

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 (590). Several studies point out at the importance of this region in emotion regulation (591-593), and in down-regulation of emotional processing (594) in normal population. Negative symptoms have been attributed to overinhibition of affective processes and maladaptive cognitive emotion regulation strategies (595). These processes were associated with increased frontal activation and volume (590, 596), while disinhibition and emotional lability have been associated with frontal lesions (597, 598). For example, Smith et al., (2013) showings that a decrease in volume of the DLPFC is associated with improvement of depression symptoms in patients with depression (599). WM connectivity abnormalities in the superior frontal executive region have been proposed to explain negative symptoms in schizophrenia (578, 600). 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 (579). 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.

Another important finding was the fact that the parietal cortex was inversely correlated with the positive symptoms. Several studies show that positive symptoms were related to deficits of

logical reasoning processes (601). Such processes are mediated by the parietal cortex (602). In accordance with these results Dazzan and colleagues (2012), found that subjects who eventually developed schizophrenia had smaller volumes in the parietal cortex (579)

According to our results, the cerebellum played an important role in positive and negative symptoms and was a major region differentiating memory accuracy between healthy controls and schizophrenia patients. These latter results are discussed in a subsequent section. The cerebellum with its cortical connections (the limbic system, the frontal, parietal, prefrontal, occipital, and temporal cortex), opens a new pathways for explaining the diversity of symptoms of schizophrenia (603) In addition, it plays a role in higher cognitive and emotional cortical functions (604). Based on our results, the cerebellum is more correlated with negative symptoms. Stoodley et al. (2010) postulated 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 (605). Our results point 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. Hallucinations and delusions were found to be associated with deficits in several cognitive processes (606) including perception and correction errors (607), source and self-monitoring (608), stimulus recognition (609), reality monitoring (610, 611).

Exploratory prediction model of the linear regression relationship between GMD and WMD with the PANSS symptoms has also produced noteworthy results. In broad lines, WMD increases were related with less hostility scores and more sever conceptual disorganization and attention deficits. Additionally, 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 (612, 613). Interestingly, the intensity of conceptual disorganization was a predicting factor of increased GMD and WMD in schizophrenia patients in our study. To our knowledge, no other study has reported such findings in schizophrenia. Similar findings have been reported in autism, where increased white matter volume was associated with language and communication deficits (614), which are fundamental elements in the construction of conceptual disorganization, however further studies are needed in schizophrenia to support this

view. In accordance with existing literature, GMD was inversely correlated with hallucinations. 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 (276, 615, 616), left thalamus, and left and right cerebellum (276) middle/inferior right prefrontal gyri (615), bilateral insula and left amygdala (616, 617).

We expected that GI values in several brain regions would be significantly correlated with the severity of symptoms, but we found only one association between occipital GI and negative symptoms. Given that overt clinical expression of some psychiatric and neurodevelopmental disorders may be a reflection of an underlying abnormality in growth of cortical convolutions (618), it is plausible that the significant decrease in the GI observed in schizophrenia is not directly related to symptoms but to the disease itself. Our findings point to abnormalities in the morphological development of the cortical layer in schizophrenia. Neurodevelopmental brain changes may be present at the onset of the illness (20, 562, 619-624), with further changes occurring during progression of schizophrenia (619, 625-629). In addition, we found that the abnormalities in GI, GMD and WMD in our group of schizophrenia patients in comparison to healthy controls were not the same regions that correlated with schizophrenia clinical symptoms. It is possible that decreases in cortical gyrification are related to other illness deficits as neurocognitive measures, and are not necessarily associated with clinical symptoms. We postulate that cognitive deficits play a role in such discrepancy. Several studies have shown abnormalities in these regions in relation with deficits in mental rotation abilities (630), IQ performance (631), language processing (632), and face recognition (633). In addition, abnormalities in the left middle temporal, the left inferior frontal and the left posterior parietal regions were found in be correlated with deficits in emotional memory accuracy in another study performed by our group (634, 635).

Behavioral findings

Schizophrenia patients showed significant deficits in all neuropsychological measures when compared to normal controls subjects including WAIS, Raven percentile, and memory recall tasks. This is consistent with numerous previous reports (137, 463, 636-641). In terms of performance on the memory task specifically, it was associated with GMD and WMD abnormalities in schizophrenia patients. As expected, patients has significantly worse at the memory accuracy task

and had significantly decreased GMD and WMD in major brain regions involved in the behavioral task. The most significant result we should first note however is the increased correlations between memory performance and the GMD and WMD in the parieto-occipital regions in schizophrenia patients compared to healthy controls. Previous work report enhanced function in higher visual areas combined with enhanced recruitment of sensory areas in schizophrenia patients during memory performance (642).

Within the regions that showed structural abnormalities in schizophrenia patients, the posterior parietal GMD and WMD especially differentiated healthy controls from schizophrenia patients in relation to the memory recall scores. This region sub-serves visuospatial attention and memory (643), and several studies have reported gray matter abnormalities including reversed asymmetry (644), reduced gray matter density (272), and impaired activity during memory retrieval tasks (645, 646) in schizophrenia. However, we observed that schizophrenia patients displayed a relationship between the memory score accuracy recall and the WM of the angular region, which is also situated in the parietal lobe. The angular gyrus is a heteromodal region involving verbal retrieval, language and semantic processing (647) as well as spatial attention and orienting (648). This makes its relation to schizophrenia particularly interesting. According to Pearlson et al., (1996), schizophrenia is associated with disturbance in the heteromodal cortex, which is considered as “higher-order parallel distributed networks of circuits, mediating complex representationally guided behaviors” (649).

When we specifically considered the temporal lobe, we observed increased correlations with the behavioral task in the GMD and WMD in healthy controls compared to schizophrenia. This is in accordance with the existing literature. For example, Rametti and colleagues (2007) have shown significant correlation between forgetting and density of the anterior hippocampus. They argued that these findings support the hypothesis of a regional atrophy within the hippocampus in schizophrenia patients (650).

Most neuroimaging studies investigating memory in schizophrenia have focused on working memory during fMRI. Significant interaction between brain function and structure has been postulated (651), however few studies have attempted to investigate the core GM and WM structures in relation to memory deficits, which are among the core endophenotypes in schizophrenia (652). Interpreting reality mostly involves remembering relative information about

a situation; therefore, understanding recall of memory dysfunction in schizophrenia is fundamental. For example, when remembering that "I was in my friend's house yesterday", a firm grounding in reality requires that I know the context in which that memory was formed.

Overall, the results of the present thesis demonstrate the presence of cortical and subcortical abnormalities in patients with schizophrenia. These abnormalities were related to schizophrenia symptoms and to cognitive and behavioral deficits.

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

Findings concerning sex differences

Structural findings

Hemispheric and regional decreases in frontal lobes in patients have been frequently reported in the literature, however only few have reported sex differences (556-558). We found that male patients had significantly lower values of the GI in the right hemisphere relative to same-sex controls, but no differences were found between female groups. It is well documented that GI decreases with age in the general population (653), and our results support these findings. However, such decreases were more severe in patients with schizophrenia, especially in males and particularly in the right hemisphere. Furthermore, only males had significant decreases associated with the duration of illness. Several studies have shown an association between severity of illness and disturbances in cerebral structure and connectivity in the right hemisphere (654).in frontal lobes (654-656), and temporal and parietal lobes (654, 656, 657) Such disturbances tend to deteriorate with duration of illness (658-662) and are worse in patients who have earlier age of onset (20, 562, 619-624). Our findings may help explain why the course of illness, prognosis, and social outcomes are often worse in males relative to females with schizophrenia.

Additional sex differences in patients included the fact that male patients had global hemispheric decreases not confined to any specific region, whereas female patients had significantly lower GI in the left frontal, bilateral temporal and left parietal lobes. These findings may reflect a more defused and generalized cortical loss in males. In comparison, females might compensate by preserving cortical gyrification in other cerebral regions. For example, Abbs et al, (2011), found that female patients 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 (553). This task correlated with the anterior cingulated volumes in same-sex healthy 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 patient 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 (303, 663, 664) 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 (663).

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 (544).

Consistently with the GI findings of sex differences in schizophrenia, examination of total GMD revealed that male patients had decreased total GMD compared to healthy males, while no differences were observed in female groups. Several studies have shown that males have more GM abnormalities than females with schizophrenia: 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 have more preserved cerebral morphology (292, 301, 517-524). Several authors have suggested that these differences are due to the neuroprotective effects of estrogen in females (339-341). The lack of differences in white matter densities between males with schizophrenia and same-sex controls was of particular interest. Recent findings show that abnormalities in white matter in patients with schizophrenia are related to disturbed sexual dimorphism rather than decreased white matter densities (512, 665).

Correlations between structures and clinical symptoms

Our findings revealed that female patients with more negative symptoms also had greater GI in the right occipital cortex, whereas male patients who had greater negative symptoms had lower GI in the left occipital cortex. As mentioned previously, few correlations where found between GI abnormalities and symptoms. Jou et al. (2005) demonstrated abnormalities in cortical gyrification in individuals at increased genetic risk of schizophrenia who are not presenting the full schizophrenia symptomatology (666). To explain these findings, a study by Onitsuka et al., (2007) showed a relation between reduced volumes in the visual association areas and hallucinations. Their study included only male schizophrenia patients (667). Bijanki et al., (2015) reported an association between increased white matter fractional anisotropy in the occipital lobe and increased score of Scale for the Assessment of Negative Symptoms (SANS) in schizophrenia patients. The authors did not report any sex differences (668). Mitelman et al., (2003) found that patients with negative symptoms and poorer outcome had significantly lower gray matter volumes in the temporal and occipital lobes compared to better outcome patients and healthy controls (669).

Of particular interest is that female patients in our study had significantly more symptoms compared to male patients, but it was males who exhibited more diffuse cortical abnormalities. In addition, females with schizophrenia had no association between total GMD, WMD, CSF, or total brain volume with any of the individual schizophrenia symptoms. Only males with schizophrenia showed an inverse correlation between ideas of grandiosity and WMD. Additionally, correlations between disorientation and WMD and attention deficits and GMD and WMD were observed 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 (512). Correlation between increased WMD and attention deficits has been reported in patients with ADHD (670). However, to our knowledge this is the first study to report such finding only in males with schizophrenia. Studies show that males with schizophrenia show more attention deficits compared to female patients (454). These findings suggest that females with schizophrenia may be less vulnerable to particular cognitive deficits compared to males with schizophrenia (455).

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 (671). Furthermore, prevalence of grandiosity was reported to be higher in males than females with early episode psychosis (672). 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 (390).

To our knowledge, this is the first study to report a direct relation between white matter density and these symptoms. Interestingly a study by Sallet et al., (2003) found correlations between cortical gyrification index and grandiosity (673). Gyrification index is a marker of degree of cortical folding which is hypothesized to represent underlying white matter volume (674). 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 (675). The white matter abnormalities are in support of neurodevelopmental disturbance that is more evident in males than females with schizophrenia.

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 further support to the important role of sex differences in schizophrenia.

Correlations between structures and cognitive performance

Importantly for the present thesis, sex differences were also observed in the third study. We used a memory task based on photos from the *International Affective Picture System (IAPS)* database. IAPS provides a standardized set of pictures for studying emotion and attention (676). Male patients showed inverse correlations between WMD and memory accuracy of negative and

positive pictures. Healthy males had GMD that positively correlated with negative pictures. Interestingly, in female groups no correlations were found.

The relatively late WM myelination and neuronal pruning of brain regions in schizophrenia might play a role in the current findings (677-679). It has been suggested that schizophrenia is a consequence of a neurodevelopmental process of synaptic overpruning (680). Highly et al., (2003) has reported distinct sex difference in schizophrenia patients, where female patients had reduced white matter volumes in the occipito-parietal region, while male patients had increased density in the same region (565). Of interest, in our study we found abnormalities in white matter densities in the occipito-parietal region in our group of schizophrenia patients. Further investigation is needed to find out if these abnormalities are sex specific.

Behavioral findings

Sex differences in our second study 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 no differences were found between female groups on the block design task. When direct comparisons were performed 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 (94, 95). Studies on healthy population show better performances in males compared to females on spacio-visual tasks (96, 97). Together these findings support the presence of an inverse sexual dimorphism in schizophrenia patients (98-100). Sex differences observed support existing literature showing males with schizophrenia have worse cognitive performance compared females with schizophrenia. Female schizophrenia have preserved language, verbal memory and visuospatial memory (455) and have better performances in processing speed and episodic memory compared to males with schizophrenia (455, 461, 462). Reasoning tasks have been closely related to the posterior parietal cortex (602). Abnormalities in this region has been reported particularly in male patients with schizophrenia (547, 553). Perturbation of normal gray matter volume asymmetry, has been observed in the left inferior parietal lobes in male patients, but

not female patients (547). In our first study, only male schizophrenia patients showed more rapid decreased GI values in the right parietal lobe in relation to duration of illness. It is proposed that females with schizophrenia compensate volumetric loss in the anterior cingulate by engaging alternative patterns between the inferior parietal and the prefrontal cortex (553). These differences in cognitive impairments may be a result of sex differences in age of onset or illness severity (37, 403, 464-471).

On the memory accuracy task, both females and males with schizophrenia performed worse than same-sex control groups on all conditions of the memory task, but no sex differences were observed in controls or in patients. This was an unexpected finding, since we anticipated that females and males with schizophrenia would perform differently; specifically that male patients would show greater deficits. We propose that the emotional component of this task played a role in decreasing the anticipated performance in female patients. We can find support for this postulation when analyzing the subjective rating results. Here clearly we observe that females with schizophrenia expressed less subjective experience to negative images compared to the same-sex controls. Additionally, difference in subjective rating disappeared when we compared females with schizophrenia and normal control males. Most studies show no sex differences in emotional experience (681, 682). Thus, our finding that female patients report less subjective experience with negative images is relatively novel. Here, we observe again an inverse sexual dimorphism in female patients with schizophrenia. In our study, males with schizophrenia subjectively rated negative images similarly to normal control males, but rated neutral images greater than both males and females controls. A meta-analyses by Cohen and Minor (2010) revealed that schizophrenia patients had preserved emotional experience but may experience strong aversive emotions when processing stimuli considered by healthy population as pleasant or neutral (681). To explain our findings, we postulate that as a way of coping with the disorder, females with schizophrenia use stress avoidance strategies to prevent exacerbation of symptoms. Studies demonstrate that patients who manage stressful events and internal stress are less likely to present sever symptoms (595, 683, 684). Emotion-focused and inhibitory coping styles against stress have been reported in healthy females more than males who use more operative coping styles (685-687). Interestingly, male patients in our study over experienced neutral images.

Overall, present studies support existing literature about abnormalities in key cortical regions implicated in schizophrenia. Sex differences in schizophrenia patients were demonstrated

throughout the three studies. Morphological differences in gyrification and in grey and white matter densities, differences in correlations between gyrification, GMD, WMD and symptoms, and differences in correlations between GMD and WMD and memory acuity. We conclude from our findings two important things. First, that sex differences in schizophrenia are present and affect the morphology, the clinical presentation of the disease and cognitive functions in patients. Secondly, that males with schizophrenia have more structural and functional abnormalities that worsen with the duration of illness compared to females with schizophrenia.

In agreement with Wang et al., (2010) our findings suggest that the core pathophysiological problem underlying symptom presentation and cognitivo-emotional processes are related to disruptive coordination of large scale brain networks and this may be affected by structural deficits. These structural deficits are strongly sex related (688).

Several elegant hypotheses have been proposed to explain sex differences in the schizophrenia brain. Crow (2008) suggested that sex differences related to psychosis are attributed to a genetic species-specific variation related to a locus on the X and Y chromosomes. Gene expression in this region is influenced by the degree of X and Y chromosomes pairing in male meiosis. This process is referred to as MSUC “meiotic suppression of unpaired chromosomes" which normally would lead to a more rapid mean rate of lateralization in females than in males (this in turn relates to the higher incidence rate of language delays and dyslexias in males). This complex theory posits that language disturbances are integral to psychosis. Lateralization or cerebral torque (where the right frontal lobe is larger than the left, while the left occipito-temporo-parietal is larger than the right) is due to the development of neural connections associated with language: from right to left in relation to the motor speech output and from left to right in relation to speech perception. Disturbance in this neural development was proposed as the basis of the genetic predisposition to psychosis, i.e. the authors suggest that schizophrenia is a result of an abnormal cerebral lateralization associated with the emergence of language in humans (571). When this hypothesis is considered in the context of brain structures, it may explain the higher levels of anomalies found in males compared to female patients in our study and the differences in the development of schizophrenia in males and females in general (572).

The influence of sex steroid hormones has also been considered (573, 574). These studies strongly suggest that the neuroprotective effects of estrogen (which influences sexual characteristics, development of the brain aminergic networks, and the ability to adapt to stressful

events) enhance the vulnerability threshold for psychosis by the downward regulation of dopamine. For example, Riecher-Rossler et al., (1994) and Hafner (2003) found that increased levels of estrogen in females with schizophrenia with normal menstrual cycles were significantly associated with lower severity of schizophrenia symptoms suggesting that that estrogen had: "a weak neuroleptic-like effect on schizophrenia symptoms" (325, 689, 690). The estrogen neuro-protective hypothesis is one of the most widely accepted explanations. Estrogens, directly or indirectly, modulates symptom expression in males and females with schizophrenia. Organizational and activational effects have been attributed to sex hormones. Organizational effects occur in the brain during the prenatal fetal phase and are stable, while activational effects are related to the level of circulating hormones (311, 312, 315, 414-421). Seeman and Lang (1990) put forward several arguments in favor of the estrogen neuro-protective hypothesis. The modulatory relation between the dopaminergic system and estrogen have been proposed to delay the onset of illness by 4-6 years is females and to cause an additional onset peak at age 40 to 45 years, when estrogen levels decrease. Males exhibit one main peak of schizophrenia onset in their late teens and early twenties. Females present with less debilitating symptoms during the first decade following onset, in thereafter their symptoms approximates that of males, particularly after menopause. Lower doses of antipsychotic treatment are effective premenopausally, perhaps due to the potentiating effect of the antidopaminergic action of estrogen, while higher doses are needed postmenopausally (417). Rendering further support to this hypothesis is the effectiveness of estrogen therapy in improving symptoms of schizophrenia (422, 423). The observed worsening of symptoms when estrogen levels drop sharply after pregnancy or during the follicular phase of the menstrual cycle (424, 425), and symptom improvement during mid-luteal phase when estrogen levels are high in females with schizophrenia directly supports this hypothesis (426-429).

In short, evidence based medicine may be fundamentally flawed because there is an ongoing failure of research tools to include sex differences in study design and analysis (691, 692). The US National Institutes of Health (NIH) issued study guidelines for the evaluation of gender differences. Their aim was to ensure that drug safety and efficacy of are adequately investigated (691-693). Over the past decade sex differences in schizophrenia are more widely acknowledged and females are more frequently studied or at least included in the protocols (694). For example, it is recognized that females might require lower doses of antipsychotic medications during their reproductive years due to antipsychotic-estradiol interactions (340-342).

Our findings support the hypothesis that possible factors contributing to the development of schizophrenia and related psychosis are slightly different in males and females and that these factors interact differently with the sexes (694).

We advocate the need to include female and male subjects in research designs in an equal manner and performing analyses and interpreting results in males and females separately.

8.2 Limitation

Even though several studies show similar results using cortical thickness and gray matter density. GI along with cortical thickness seem to be more sensitive to genetic and phenotypic differences than grey matter volume (695). Density mapping may be influenced by diagnostic differences in extra-cortical CSF and surface curvature/complexity (554).

Even though patients with past or present diagnosis of drug and alcohol abuse were excluded from the study, chronic substance and alcohol *misuse* is reported more frequently in male than female schizophrenia patients, and may contribute to the greater changes observed in male patients.

Finally, as gyrification decreases in both healthy controls and patients were observed, gyrification is a more ambiguous marker as it is difficult to isolate factors of gyrification decline related to healthy aging from those related to disease (confounded by disease progression, different behavioral factors, and substance/medication exposure). However, sex differences in patients with schizophrenia remained consistent after controlling for these variables.

Since our DARTEL VBM study cannot be used to directly infer GM-WM connectivity and projections, our data do not immediately address the question of whether schizophrenia patients alternatively use occipito-parietal network instead of fronto-parietal network (i.e., re-arranged connections). Future studies are needed to differentiate network dysfunction from previously observed GM and WM abnormalities of the fronto-temporal, occipito-parietal and cerebellar-fronto hubs, and to link such disturbed connectivity patterns with specific clinical and cognitivo-behavioral phenotypes of schizophrenia. Overall, our findings may help to elucidate key cortical regions implicating loss of GM/WM volume/density, which may play a role in disturbed cerebral connectivity network fundamental to memory recall and modulation of symptoms. By taking into account the patients' sex in our studies; we demonstrated that sex differences influence results and that separating males from females in experimental designs may help a better understanding of the illness

Another limitation of the presented studies is a potential effect of antipsychotic medication (past and current). We specify that all our 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 the patients received at least one atypical antipsychotic (chlorpromazine equivalence was calculated) (696).

Another limitation is that our list of assessments was by no means exhaustive. We used only one scale to assess the positive and negative symptoms (i.e., the PANSS). We anticipate in our future research the need to investigate that regions correlating with positive and negative symptoms assessed by PANSS remain consistent using other symptom assessment scales such as "Symptom rating scales and outcome in schizophrenia" (697)

Considerable heterogeneity remains across studies investigating changes in GM and WM volume structures in schizophrenia. Heterogeneous symptoms may contribute to inconsistent findings. In future studies, we advocate to group large number of patients by symptom dimensions, which map on the emotional, cognitive, and psychomotor dimensions. Studies using the symptoms' dimensional approach in schizophrenia may be useful for elucidating the core pathophysiology of this illness and in reducing heterogeneity of brain morphological endophenotypes in schizophrenia. We emphasize the importance of sex differences here. As seen in our first and second studies, same symptoms seem to be related differently to the brain in males and females with schizophrenia. Thus, studies need to investigate symptom dimensions in males and females separately.

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.

9 Conclusion

Structure abnormalities in patients with schizophrenia were detected in the cerebral cortex and white and gray matter densities when compared to healthy controls. These abnormalities were more robust in male patients, and worsened with the progress of the disease. Females with schizophrenia had fewer deviations from healthy females, and even when important abnormalities were detected, females with schizophrenia seemed to recruit/compensate by the preservation of alternative cerebral regions. Furthermore, we emphasize that age of onset and duration of illness seems to influence cerebral structures to a greater extent in males than in females with schizophrenia. We suggest that the core pathophysiological problem underlying symptom presentation and cognitivo-emotional processes are related to disruptive coordination of large-scale brain networks (688), and this may be affected by structural deficits. These structural deficits are strongly sex related. Accordingly, we advocate that future studies should include large samples of males and females with schizophrenia. Using connectomes or brain networks approaches to investigate the relationship between sex and brain function in schizophrenia is encouraged. Despite the diligent efforts to control for age, sex, medications, disease onset, the heterogeneity of symptoms, might have influenced our findings. As previously advocated by our group (178, 179, 698, 699), future studies should examine large number of patients by symptom clusters, including emotional, cognitive and psychomotor dimensions. In this work, we advocate that considering sex of patients in schizophrenia is a crucial factor to be considered in the design of research studies.

10 Clinical and research implications

Our overall findings point out to the importance of sex in modulating the clinical and functional presentation of schizophrenia. Controlling for covariates such as age, duration of illness, social status, etc. is insufficient thus future studies in schizophrenia should systematically separate between males and females, if we wish to understand this complex and devastating mental illness. As emphasized in his visionary paper V*ive la Difference* Shon Lewis (1992) advanced that using sex for subtyping schizophrenia, is a - reliable, stable and valid - an immutable sociodemographic variable (360). Clinically, we advance that therapeutic approaches need to be customized to the sex of the patient. Therapy type, treatment dose, and duration need to be reviewed in light of the significant and morphological sex differences in schizophrenia. Knowing the sex of the patient, may help determine the therapeutic approach and disease trajectory. We can adapt health care according to her or his needs, understand risks, and improve prognosis. This work puts forward the following major conclusions: 1- Sex differences in schizophrenia are present in the major aspects of the disease, and these differences remain while using different methods. 2- Sex in schizophrenia is a crucial factor to be considered in the design of schizophrenia studies. 3- Results from studies grouping both males and females with schizophrenia should be interpreted with caution. 4- On a clinical level, taking sex differences in consideration is important if we wish to address the individuality of each of our patients and help improve their quality of life.

11 References

1. Bleuler E. Dementia Praecox or the Group of Schizophrenias. . (translated by J Zinkin, published in 1950) 1950.

2. Kraepelin E, editor. Dementia praecox and paraphrenia. Huntington, New York,: Publishing Co. Inc., ; 1919/1971.

3. Schneider K. Clinical Psychopathology. M. W. Hamilton (trans.), editor. New York:: Grune and Stratton 1959.

4. Moreno C, Nuevo R, Chatterji S, Verdes E, Arango C, Ayuso-Mateos JL. Psychotic symptoms are associated with physical health problems independently of a mental disorder diagnosis: results from the WHO World Health Survey. World Psychiatry. 2013;12(3):251-7.

5. Miller EE, Grosberg BM, Crystal SC, Robbins MS. Auditory hallucinations associated with migraine: Case series and literature review. Cephalalgia : an international journal of headache. 2014.

6. Arciniegas DB, Topkoff JL, Held K, Frey L. Psychosis Due to Neurologic Conditions. Current treatment options in neurology. 2001;3(4):347-66.

7. Sorensen K, Nielsen J. Twenty psychotic males with Klinefelter's syndrome. Acta psychiatrica Scandinavica. 1977;56(4):249-55.

8. Sorensen K, Nielsen J. Reactive paranoid psychosis in a 47, XYY male. Acta psychiatrica Scandinavica. 1977;55(3):233-6.

9. Bacalman S, Farzin F, Bourgeois JA, Cogswell J, Goodlin-Jones BL, Gane LW, et al. Psychiatric phenotype of the fragile X-associated tremor/ataxia syndrome (FXTAS) in males: newly described fronto-subcortical dementia. The Journal of clinical psychiatry. 2006;67(1):87-94.

10. Petty LK, Ornitz EM, Michelman JD, Zimmerman EG. Autistic children who become schizophrenic. Arch Gen Psychiatry. 1984;41(2):129-35.

11. Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, "just the facts" 4. Clinical features and conceptualization. Schizophr Res. 2009;110(1-3):1-23.

12. Green MF. Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. J Clin Psychiatry. 2006;67 Suppl 9:3-8; discussion 36-42.

13. Rund BR, Borg NE. Cognitive deficits and cognitive training in schizophrenic patients: a review. Acta Psychiatr Scand. 1999;100(2):85-95.

14. Leung A, Chue P. Sex differences in schizophrenia, a review of the literature. Acta Psychiatr Scand Suppl. 2000;401:3-38.

15. Hafner H, Hambrecht M, Loffler W, Munk-Jorgensen P, Riecher-Rossler A. Is schizophrenia a disorder of all ages? A comparison of first episodes and early course across the life-cycle. Psychol Med. 1998;28(2):351-65.

16. Moberg PJ, Roalf DR, Gur RE, Turetsky BI. Smaller nasal volumes as stigmata of aberrant neurodevelopment in schizophrenia. Am J Psychiatry. 2004;161(12):2314-6.

17. Gur RC, Gunning-Dixon FM, Turetsky BI, Bilker WB, Gur RE. Brain region and sex differences in age association with brain volume: a quantitative MRI study of healthy young adults. Am J Geriatr Psychiatry. 2002;10(1):72-80.

18. Gur RE, Kohler C, Turetsky BI, Siegel SJ, Kanes SJ, Bilker WB, et al. A sexually dimorphic ratio of orbitofrontal to amygdala volume is altered in schizophrenia. Biol Psychiatry. 2004;55(5):512-7.

19. Goldstein JM, Seidman LJ, O'Brien LM, Horton NJ, Kennedy DN, Makris N, et al. Impact of normal sexual dimorphisms on sex differences in structural brain abnormalities in schizophrenia assessed by magnetic resonance imaging. Arch Gen Psychiatry. 2002;59(2):154-64.

20. Frazier JA, Hodge SM, Breeze JL, Giuliano AJ, Terry JE, Moore CM, et al. Diagnostic and sex effects on limbic volumes in early-onset bipolar disorder and schizophrenia. Schizophr Bull. 2008;34(1):37-46.

21. Grossman LS, Harrow M, Rosen C, Faull R, Strauss GP. Sex differences in schizophrenia and other psychotic disorders: a 20-year longitudinal study of psychosis and recovery. Compr Psychiatry. 2008;49(6):523-9.

22. Lewis DA, Lieberman JA. Catching up on schizophrenia: natural history and neurobiology. Neuron. 2000;28(2):325-34.

23. Funahashi T, Ibuki Y, Domon Y, Nishimura T, Akehashi D, Sugiura H. A clinical study on suicide among schizophrenics. Psychiatry Clin Neurosci. 2000;54(2):173-9.

24. Bertelsen M, Jeppesen P, Petersen L, Thorup A, Ohlenschlaeger J, le Quach P, et al. Suicidal behaviour and mortality in first-episode psychosis: the OPUS trial. Br J Psychiatry Suppl. 2007;51:s140-6.

25. Andreasen NC, Carpenter WT, Jr. Diagnosis and classification of schizophrenia. Schizophr Bull. 1993;19(2):199-214.

26. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gen Psychiatry. 2007;64(10):1123-31.

27. McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiologic reviews. 2008;30:67-76.

28. American Psychiatric Association A. Diagnostic and Statistical Manual of Mental Disorders (DSM 5). Arlington, VA: APA; 2013.

29. Moller HJ, Bandelow B, Bauer M, Hampel H, Herpertz SC, Soyka M, et al. DSM-5 reviewed from different angles: goal attainment, rationality, use of evidence, consequences-part 2: bipolar disorders, schizophrenia spectrum disorders, anxiety disorders, obsessive-compulsive disorders, trauma- and stressor-related disorders, personality disorders, substance-related and addictive disorders, neurocognitive disorders. European archives of psychiatry and clinical neuroscience. 2014.

30. American Psychiatric Association A. Highlights of Changes from DSM-IV-TR to DSM-5. APA. 2013.

31. Nemeroff CB, Weinberger D, Rutter M, MacMillan HL, Bryant RA, Wessely S, et al. DSM-5: a collection of psychiatrist views on the changes, controversies, and future directions. BMC medicine. 2013;11:202.

32. Henderson S, Malhi GS. Swan song for schizophrenia? The Australian and New Zealand journal of psychiatry. 2014;48(4):302-5.

33. Schultze-Lutter F, Schimmelmann BG. [Changes to Schizophrenia Spectrum and other psychotic disorders in DSM-5]. Zeitschrift fur Kinder- und Jugendpsychiatrie und Psychotherapie. 2014;42(3):193-202.

34. Tan N, van Os J. [The schizophrenia spectrum and other psychotic disorders in the DSM-5]. Tijdschrift voor psychiatrie. 2014;56(3):167-72.

35. Savill M, Banks C, Khanom H, Priebe S. Do negative symptoms of schizophrenia change over time? A meta-analysis of longitudinal data. Psychol Med. 2014:1-15.

36. Addington J, Addington D. Positive and negative symptoms of schizophrenia. Their course and relationship over time. Schizophr Res. 1991;5(1):51-9.

37. Addington J, Addington D, Maticka-Tyndale E. Cognitive functioning and positive and negative symptoms in schizophrenia. Schizophr Res. 1991;5(2):123-34.

38. Andreasen NC, Flaum M. Schizophrenia: the characteristic symptoms. Schizophr Bull. 1991;17(1):27-49.

39. Blanchard JJ, Cohen AS. The structure of negative symptoms within schizophrenia: implications for assessment. Schizophr Bull. 2006;32(2):238-45.

40. Carbon M, Correll CU. Thinking and acting beyond the positive: the role of the cognitive and negative symptoms in schizophrenia. CNS spectrums. 2014:1-19.

41. Buck BE, Healey KM, Gagen EC, Roberts DL, Penn DL. Social cognition in schizophrenia: factor structure, clinical and functional correlates. J Ment Health. 2016:1-8.

42. Loughland C, Draganic D, McCabe K, Richards J, Nasir A, Allen J, et al. Australian Schizophrenia Research Bank: a database of comprehensive clinical, endophenotypic and genetic data for aetiological studies of schizophrenia. The Australian and New Zealand journal of psychiatry. 2010;44(11):1029-35.

43. Tsang HW, Leung AY, Chung RC, Bell M, Cheung WM. Review on vocational predictors: a systematic review of predictors of vocational outcomes among individuals with schizophrenia: an update since 1998. The Australian and New Zealand journal of psychiatry. 2010;44(6):495-504.

44. Best MW, Grossman M, Oyewumi LK, Bowie CR. Examination of the Positive and Negative Syndrome Scale factor structure and longitudinal relationships with functioning in early psychosis. Early intervention in psychiatry. 2014.

45. Lim J, Lee SA, Lam M, Rapisarda A, Kraus M, Keefe RS, et al. The relationship between negative symptom subdomains and cognition. Psychol Med. 2016:1-9.

46. Snyder SH. The dopamine hypothesis of schizophrenia: focus on the dopamine receptor. The American journal of psychiatry. 1976;133(2):197-202.

47. Laruelle M, Abi-Dargham A. Dopamine as the wind of the psychotic fire: new evidence from brain imaging studies. Journal of psychopharmacology. 1999;13(4):358-71.

48. Laruelle M, Abi-Dargham A, Gil R, Kegeles L, Innis R. Increased dopamine transmission in schizophrenia: relationship to illness phases. Biol Psychiatry. 1999;46(1):56-72.

49. Weinberger DRaW, R.J., editor. Brain morphology in schizophrenia: in vivo studies. New York: Oxford University Press; 1982.

50. Ho BC, Andreasen N, Flaum M. Dependence on public financial support early in the course of schizophrenia. Psychiatric services. 1997;48(7):948-50.

51. Murray CJ, Lopez AD. Evidence-based health policy--lessons from the Global Burden of Disease Study. Science. 1996;274(5288):740-3.

52. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet. 2013;382(9904):1575-86.

53. Bhugra D. The global prevalence of schizophrenia. PLoS Med. 2005;2(5):e151; quiz e75.

54. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry. 1994;51(1):8-19.

55. Jablensky A, Sartorius N, Ernberg G, Anker M, Korten A, Cooper JE, et al. Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. Psychological medicine Monograph supplement. 1992;20:1-97.

56. Cohen A, Patel V, Thara R, Gureje O. Questioning an axiom: better prognosis for schizophrenia in the developing world? Schizophr Bull. 2008;34(2):229-44.

57. Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. PLoS Med. 2005;2(5):e141.

58. Rice DP. The economic impact of schizophrenia. The Journal of clinical psychiatry. 1999;60 Suppl 1:4-6; discussion 28-30.

59. Essock S, Frisman L, Covell N. The economics of the treatment of schizophrenia. In: Kenneth L. Davis DC, Joseph T. Coyle, and Charles Nemeroff. , editor. Neuropsychopharmacology: The Fifth Generation of Progress. Philadelphia, Pennsylvania: American College of Neuropsychopharmacology, Lippincott, Williams, & Wilkins; 2002.

60. Tandon R, Keshavan MS, Nasrallah HA. Schizophrenia, "Just the Facts": what we know in 2008 part 1: overview. Schizophr Res. 2008;100(1-3):4-19.

61. Bray I, Waraich P, Jones W, Slater S, Goldner EM, Somers J. Increase in schizophrenia incidence rates: findings in a Canadian cohort born 1975-1985. Social psychiatry and psychiatric epidemiology. 2006;41(8):611-8.

62. Woogh C. Is schizophrenia on the decline in Canada? Canadian journal of psychiatry Revue canadienne de psychiatrie. 2001;46(1):61-7.

63. Sham PC, MacLean CJ, Kendler KS. Risk of schizophrenia and age difference with older siblings. Evidence for a maternal viral infection hypothesis? The British journal of psychiatry : the journal of mental science. 1993;163:627-33.

64. Weinberger DR. From neuropathology to neurodevelopment. Lancet. 1995;346(8974):552-7.

65. Walker EF, Brennan PA, Esterberg M, Brasfield J, Pearce B, Compton MT. Longitudinal changes in cortisol secretion and conversion to psychosis in at-risk youth. Journal of abnormal psychology. 2010;119(2):401-8.

66. Gourion D, Goldberger C, Olie JP, Loo H, Krebs MO. Neurological and morphological anomalies and the genetic liability to schizophrenia: a composite phenotype. Schizophr Res. 2004;67(1):23-31.

67. Wolf SS, Weinberger DR. Schizophrenia: a new frontier in developmental neurobiology. Israel journal of medical sciences. 1996;32(1):51-5.

68. Maki P, Veijola J, Jones PB, Murray GK, Koponen H, Tienari P, et al. Predictors of schizophrenia--a review. British medical bulletin. 2005;73-74:1-15.

69. Isohanni M, Lauronen E, Moilanen K, Isohanni I, Kemppainen L, Koponen H, et al. Predictors of schizophrenia: evidence from the Northern Finland 1966 Birth Cohort and other sources. Br J Psychiatry Suppl. 2005;48:s4-7.

70. Finke RA, Kosslyn SM. Mental imagery acuity in the peripheral visual field. J Exp Psychol Hum Percept Perform. 1980;6(1):126-39.

71. Fatemi SH, Folsom TD. The neurodevelopmental hypothesis of schizophrenia, revisited. Schizophr Bull. 2009;35(3):528-48.

72. Rapoport JL, Addington AM, Frangou S, Psych MR. The neurodevelopmental model of schizophrenia: update 2005. Molecular psychiatry. 2005;10(5):434-49.

73. Rapoport JL, Addington A, Frangou S. The neurodevelopmental model of schizophrenia: what can very early onset cases tell us? Current psychiatry reports. 2005;7(2):81-2.

74. Fatemi SH, Pearce DA, Brooks AI, Sidwell RW. Prenatal viral infection in mouse causes differential expression of genes in brains of mouse progeny: a potential animal model for schizophrenia and autism. Synapse. 2005;57(2):91-9.

75. Keshavan MS, Hogarty GE. Brain maturational processes and delayed onset in schizophrenia. Development and psychopathology. 1999;11(3):525-43.

76. Keshavan MS. Development, disease and degeneration in schizophrenia: a unitary pathophysiological model. J Psychiatr Res. 1999;33(6):513-21.

77. Walker EF, Diforio D. Schizophrenia: a neural diathesis-stress model. Psychological review. 1997;104(4):667-85.

78. Helle S, Gjestad R, Johnsen E, Kroken RA, Jorgensen HA, Loberg EM. Cognitive changes in patients with acute phase psychosis-Effects of illicit drug use. Psychiatry research. 2014.

79. Jonsson AJ, Birgisdottir H, Sigurdsson E. [Does the use of cannabis increase the risk for psychosis and the development of schizophrenia?]. Laeknabladid. 2014;100(9):443-51.

80. Limosin F. Neurodevelopmental and environmental hypotheses of negative symptoms of schizophrenia. BMC Psychiatry. 2014;14:88.

81. Fatemi SH, Folsom TD. The neurodevelopmental hypothesis of schizophrenia, revisited. Schizophr Bull. 2009;35(3):528-48.

82. Williams HJ, Owen MJ, O'Donovan MC. Schizophrenia genetics: new insights from new approaches. Br Med Bull. 2009;91:61-74.

83. O'Donovan MC, Craddock NJ, Owen MJ. Genetics of psychosis; insights from views across the genome. Hum Genet. 2009;126(1):3-12.

84. O'Donovan MC, Craddock N, Owen MJ. Strong evidence for multiple psychosis susceptibility genes - a rejoinder to Crow. Psychol Med. 2009;39(1):170-1.

85. Sawa A, Snyder SH. Schizophrenia: diverse approaches to a complex disease. Science. 2002;296(5568):692-5.

86. Abi-Dargham A, Meyer JM. Schizophrenia: the role of dopamine and glutamate. The Journal of clinical psychiatry. 2014;75(3):274-5.

87. Demjaha A, Egerton A, Murray RM, Kapur S, Howes OD, Stone JM, et al. Antipsychotic treatment resistance in schizophrenia associated with elevated glutamate levels but normal dopamine function. Biol Psychiatry. 2014;75(5):e11-3.

88. Laruelle M. Schizophrenia: from dopaminergic to glutamatergic interventions. Current opinion in pharmacology. 2014;14:97-102.

89. Taylor SF, Demeter E, Phan KL, Tso IF, Welsh RC. Abnormal GABAergic function and negative affect in schizophrenia. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2014;39(4):1000-8.

90. Seeman MV, Seeman P. Is schizophrenia a dopamine supersensitivity psychotic reaction? Prog Neuropsychopharmacol Biol Psychiatry. 2014;48:155-60.

91. Seeman P. Schizophrenia and dopamine receptors. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2013;23(9):999-1009.

92. Kendler KS, Diehl SR. The genetics of schizophrenia: a current, genetic-epidemiologic perspective. Schizophr Bull. 1993;19(2):261-85.

93. Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch Gen Psychiatry. 2003;60(12):1187-92.

94. Cardno AG, Gottesman, II. Twin studies of schizophrenia: from bow-and-arrow concordances to star wars Mx and functional genomics. American journal of medical genetics. 2000;97(1):12-7.

95. Cardno AG, Rijsdijk FV, West RM, Gottesman, II, Craddock N, Murray RM, et al. A twin study of schizoaffective-mania, schizoaffective-depression, and other psychotic syndromes. Am J Med Genet B Neuropsychiatr Genet. 2012;159B(2):172-82.

96. Ettinger U, Schmechtig A, Toulopoulou T, Borg C, Orrells C, Owens S, et al. Prefrontal and striatal volumes in monozygotic twins concordant and discordant for schizophrenia. Schizophr Bull. 2012;38(1):192-203.

97. Hulshoff Pol HE, van Baal GC, Schnack HG, Brans RG, van der Schot AC, Brouwer RM, et al. Overlapping and segregating structural brain abnormalities in twins with schizophrenia or bipolar disorder. Arch Gen Psychiatry. 2012;69(4):349-59.

98. Nenadic I, Langbein K, Weisbrod M, Maitra R, Rzanny R, Gussew A, et al. 31P-MR spectroscopy in monozygotic twins discordant for schizophrenia or schizoaffective disorder. Schizophr Res. 2012;134(2-3):296-7.

99. Riley B, Kendler KS. Molecular genetic studies of schizophrenia. European journal of human genetics : EJHG. 2006;14(6):669-80.

100. Takei N, Van Os J, Murray RM. Maternal exposure to influenza and risk of schizophrenia: a 22 year study from The Netherlands. J Psychiatr Res. 1995;29(6):435-45.

101. Mortensen PB, Pedersen CB, Westergaard T, Wohlfahrt J, Ewald H, Mors O, et al. Effects of family history and place and season of birth on the risk of schizophrenia. N Engl J Med. 1999;340(8):603-8.

102. Lichtermann D, Karbe E, Maier W. The genetic epidemiology of schizophrenia and of schizophrenia spectrum disorders. European archives of psychiatry and clinical neuroscience. 2000;250(6):304-10.

103. Sun J, Jia P, Fanous AH, van den Oord E, Chen X, Riley BP, et al. Schizophrenia gene networks and pathways and their applications for novel candidate gene selection. PLoS One. 2010;5(6):e11351.

104. Meier SM, Petersen L, Pedersen MG, Arendt MC, Nielsen PR, Mattheisen M, et al. Obsessive-compulsive disorder as a risk factor for schizophrenia: a nationwide study. JAMA psychiatry. 2014;71(11):1215-21.

105. McGrath J. Migrant status, vitamin D and risk of schizophrenia. Psychol Med. 2011;41(4):892-3; author reply 4.

106. Mittal VA, Ellman LM, Cannon TD. Gene-environment interaction and covariation in schizophrenia: the role of obstetric complications. Schizophr Bull. 2008;34(6):1083-94.

107. van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. Psychol Med. 2009;39(2):179-95.

108. Crow TJ. Mutation and psychosis: a suggested explanation of seasonality of birth. Psychol Med. 1987;17(4):821-8.

109. Bergen SE, O'Dushlaine CT, Lee PH, Fanous AH, Ruderfer DM, Ripke S, et al. Genetic modifiers and subtypes in schizophrenia: investigations of age at onset, severity, sex and family history. Schizophr Res. 2014;154(1-3):48-53.

110. Antonova E, Kumari V, Morris R, Halari R, Anilkumar A, Mehrotra R, et al. The relationship of structural alterations to cognitive deficits in schizophrenia: a voxel-based morphometry study. Biol Psychiatry. 2005;58(6):457-67.

111. Garrity AG, Pearlson GD, McKiernan K, Lloyd D, Kiehl KA, Calhoun VD. Aberrant "default mode" functional connectivity in schizophrenia. The American journal of psychiatry. 2007;164(3):450-7.

112. Hemsley DR. The development of a cognitive model of schizophrenia: placing it in context. Neuroscience and biobehavioral reviews. 2005;29(6):977-88.

113. Park S, Thakkar KN. "Splitting of the mind" revisited: recent neuroimaging evidence for functional dysconnection in schizophrenia and its relation to symptoms. The American journal of psychiatry. 2010;167(4):366-8.

114. Rapoport JL, Giedd JN, Gogtay N. Neurodevelopmental model of schizophrenia: update 2012. Molecular psychiatry. 2012;17(12):1228-38.

115. Friston KJ, Frith CD. Schizophrenia: a disconnection syndrome? Clinical neuroscience. 1995;3(2):89-97.

116. Shenton ME, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. Schizophr Res. 2001;49(1-2):1-52.

117. Stephan KE, Baldeweg T, Friston KJ. Synaptic plasticity and dysconnection in schizophrenia. Biol Psychiatry. 2006;59(10):929-39.

118. Dolan RJ. Emotion, cognition, and behavior. Science. 2002;298(5596):1191-4.

119. Park SJ, Shin JI, Eisenhut M. Cognitive decline in patients with pneumonia: a role for IL-2? American journal of respiratory and critical care medicine. 2014;189(6):755-6.

120. Phelps EA. Emotion and cognition: insights from studies of the human amygdala. Annual review of psychology. 2006;57:27-53.

121. Reichenberg A. The assessment of neuropsychological functioning in schizophrenia. Dialogues Clin Neurosci. 2010;12(3):383-92.

122. Hagh-Shenas H, Toobai S, Makaremi A. Selective, sustained, and shift in attention in patients with diagnoses of schizophrenia. Percept Mot Skills. 2002;95(3 Pt 2):1087-95.

123. Smith GL, Large MM, Kavanagh DJ, Karayanidis F, Barrett NA, Michie PT, et al. Further evidence for a deficit in switching attention in schizophrenia. Journal of abnormal psychology. 1998;107(3):390-8.

124. Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology. 1998;12(3):426-45.

125. Gur RE, Turetsky BI, Loughead J, Snyder W, Kohler C, Elliott M, et al. Visual attention circuitry in schizophrenia investigated with oddball event-related functional magnetic resonance imaging. The American journal of psychiatry. 2007;164(3):442-9.

126. Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. Arch Gen Psychiatry. 2009;66(8):811-22.

127. Fioravanti M, Bianchi V, Cinti ME. Cognitive deficits in schizophrenia: an updated metanalysis of the scientific evidence. BMC Psychiatry. 2012;12:64.

128. Saykin AJ, Gur RC, Gur RE, Mozley PD, Mozley LH, Resnick SM, et al. Neuropsychological function in schizophrenia. Selective impairment in memory and learning. Arch Gen Psychiatry. 1991;48(7):618-24.

129. Gur RC, Mozley PD, Resnick SM, Gottlieb GL, Kohn M, Zimmerman R, et al. Gender differences in age effect on brain atrophy measured by magnetic resonance imaging. Proc Natl Acad Sci U S A. 1991;88(7):2845-9.

130. Nuechterlein KH, Barch DM, Gold JM, Goldberg TE, Green MF, Heaton RK. Identification of separable cognitive factors in schizophrenia. Schizophr Res. 2004;72(1):29-39.

131. McKenna PJ, Tamlyn D, Lund CE, Mortimer AM, Hammond S, Baddeley AD. Amnesic syndrome in schizophrenia. Psychol Med. 1990;20(4):967-72.

132. Goldberg TE, Weinberger DR, Berman KF, Pliskin NH, Podd MH. Further evidence for dementia of the prefrontal type in schizophrenia? A controlled study of teaching the Wisconsin Card Sorting Test. Arch Gen Psychiatry. 1987;44(11):1008-14.

133. Evans JD, Heaton RK, Paulsen JS, Palmer BW, Patterson T, Jeste DV. The relationship of neuropsychological abilities to specific domains of functional capacity in older schizophrenia patients. Biol Psychiatry. 2003;53(5):422-30.

134. Frith CD, Leary J, Cahill C, Johnstone EC. Performance on psychological tests. Demographic and clinical correlates of the results of these tests. Br J Psychiatry Suppl. 1991(13):26-9, 44-6.

135. Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophr Bull. 2000;26(1):119-36.

136. Goldberg TE, Weinberger DR, Berman KF, Pliskin NH, Podd MH. Further evidence for dementia of the prefrontal type in schizophrenia? A controlled study of teaching the Wisconsin Card Sorting Test. Arch Gen Psychiatry. 1987;44(11):1008-14.

137. Luck D, Danion JM, Marrer C, Pham BT, Gounot D, Foucher J. Abnormal medial temporal activity for bound information during working memory maintenance in patients with schizophrenia. Hippocampus. 2010;20(8):936-48.

138. Achim AM, Lepage M. Episodic memory-related activation in schizophrenia: meta-analysis. The British journal of psychiatry : the journal of mental science. 2005;187:500-9.

139. Nelson MD, Saykin AJ, Flashman LA, Riordan HJ. Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging: a meta-analytic study. Arch Gen Psychiatry. 1998;55(5):433-40.

140. Weiss AP, Dewitt I, Goff D, Ditman T, Heckers S. Anterior and posterior hippocampal volumes in schizophrenia. Schizophr Res. 2005;73(1):103-12.

141. Wheeler AL, Voineskos AN. A review of structural neuroimaging in schizophrenia: from connectivity to connectomics. Frontiers in human neuroscience. 2014;8:653.

142. Wright IC, Rabe-Hesketh S, Woodruff PW, David AS, Murray RM, Bullmore ET. Meta-analysis of regional brain volumes in schizophrenia. The American journal of psychiatry. 2000;157(1):16-25.

143. Volk DW, Lewis DA. Early developmental disturbances of cortical inhibitory neurons: contribution to cognitive deficits in schizophrenia. Schizophr Bull. 2014;40(5):952-7.

144. Barkl SJ, Lah S, Harris AW, Williams LM. Facial emotion identification in early-onset and first-episode psychosis: a systematic review with meta-analysis. Schizophr Res. 2014;159(1):62-9.

145. Berenbaum H, Oltmanns TF. Emotional experience and expression in schizophrenia and depression. Journal of abnormal psychology. 1992;101(1):37-44.

146. Chan RC, Li H, Cheung EF, Gong QY. Impaired facial emotion perception in schizophrenia: a meta-analysis. Psychiatry research. 2010;178(2):381-90.

147. Cutting J. Judgement of emotional expression in schizophrenics. The British journal of psychiatry : the journal of mental science. 1981;139:1-6.

148. Gur RC, Schroeder L, Turner T, McGrath C, Chan RM, Turetsky BI, et al. Brain activation during facial emotion processing. Neuroimage. 2002;16(3 Pt 1):651-62.

149. Heimberg C, Gur RE, Erwin RJ, Shtasel DL, Gur RC. Facial emotion discrimination: III. Behavioral findings in schizophrenia. Psychiatry research. 1992;42(3):253-65.

150. Johnston PJ, Katsikitis M, Carr VJ. A generalised deficit can account for problems in facial emotion recognition in schizophrenia. Biological psychology. 2001;58(3):203-27.

151. Kohler CG, Walker JB, Martin EA, Healey KM, Moberg PJ. Facial emotion perception in schizophrenia: a meta-analytic review. Schizophr Bull. 2010;36(5):1009-19.

152. Paradiso S, Robinson RG, Boles Ponto LL, Watkins GL, Hichwa RD. Regional cerebral blood flow changes during visually induced subjective sadness in healthy elderly persons. J Neuropsychiatry Clin Neurosci. 2003;15(1):35-44.

153. Schneider F, Weiss U, Kessler C, Salloum JB, Posse S, Grodd W, et al. Differential amygdala activation in schizophrenia during sadness. Schizophr Res. 1998;34(3):133-42.

154. Limpert C, and X. Amador. . Negative symptoms and the experience of emotion. McEvoy eRSEKaJ, editor. Washington D.C: American Psychiatric Press; 2001.

155. Habel U, Gur RC, Mandal MK, Salloum JB, Gur RE, Schneider F. Emotional processing in schizophrenia across cultures: standardized measures of discrimination and experience. Schizophr Res. 2000;42(1):57-66.

156. Versola-Russo J. Cultural and Demographic Factors of Schizophrenia. International Journal of Psychosocial Rehabilitation 2006;10 ((2)):89-103.

157. Archer J, Hay DC, Young AW. Face processing in psychiatric conditions. The British journal of clinical psychology / the British Psychological Society. 1992;31 (Pt 1):45-61.

158. Feinberg TE, Rifkin A, Schaffer C, Walker E. Facial discrimination and emotional recognition in schizophrenia and affective disorders. Arch Gen Psychiatry. 1986;43(3):276-9.

159. Kohler CG, Bilker W, Hagendoorn M, Gur RE, Gur RC. Emotion recognition deficit in schizophrenia: association with symptomatology and cognition. Biol Psychiatry. 2000;48(2):127-36.

160. Sison CE, Alpert M, Fudge R, Stern RM. Constricted expressiveness and psychophysiological reactivity in schizophrenia. J Nerv Ment Dis. 1996;184(10):589-97.

161. Sweet LH, Primeau M, Fichtner CG, Lutz G. Dissociation of affect recognition and mood state from blunting in patients with schizophrenia. Psychiatry research. 1998;81(3):301-8.

162. Gessler S, Cutting J, Frith CD, Weinman J. Schizophrenic inability to judge facial emotion: a controlled study. The British journal of clinical psychology / the British Psychological Society. 1989;28 (Pt 1):19-29.

163. Lee KH, Farrow TF, Spence SA, Woodruff PW. Social cognition, brain networks and schizophrenia. Psychological medicine. 2004;34(3):391-400.

164. Savla GN, Vella L, Armstrong CC, Penn DL, Twamley EW. Deficits in domains of social cognition in schizophrenia: a meta-analysis of the empirical evidence. Schizophr Bull. 2013;39(5):979-92.

165. Dowd EC, Barch DM. Anhedonia and emotional experience in schizophrenia: neural and behavioral indicators. Biol Psychiatry. 2010;67(10):902-11.

166. Lepage M, Sergerie K, Benoit A, Czechowska Y, Dickie E, Armony JL. Emotional face processing and flat affect in schizophrenia: functional and structural neural correlates. Psychol Med. 2011;41(9):1833-44.

167. Foucher JR, Luck D, Marrer C, Pham BT, Gounot D, Vidailhet P, et al. fMRI working memory hypo-activations in schizophrenia come with a coupling deficit between arousal and cognition. Psychiatry research. 2011;194(1):21-9.

168. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception II: Implications for major psychiatric disorders. Biol Psychiatry. 2003;54(5):515-28.

169. Gur RE, McGrath C, Chan RM, Schroeder L, Turner T, Turetsky BI, et al. An fMRI study of facial emotion processing in patients with schizophrenia. The American journal of psychiatry. 2002;159(12):1992-9.

170. Kosaka H, Omori M, Murata T, Iidaka T, Yamada H, Okada T, et al. Differential amygdala response during facial recognition in patients with schizophrenia: an fMRI study. Schizophr Res. 2002;57(1):87-95.

171. Andreasen NC, Olsen S. Negative v positive schizophrenia. Definition and validation. Arch Gen Psychiatry. 1982;39(7):789-94.

172. Kline JS, Smith JE, Ellis HC. Paranoid and nonparanoid schizophrenic processing of facially displayed affect. J Psychiatr Res. 1992;26(3):169-82.

173. Lewis SF, Garver DL. Treatment and diagnostic subtype in facial affect recognition in schizophrenia. J Psychiatr Res. 1995;29(1):5-11.

174. Anglin D, Stanford AD, Harkavy-Friedman JM, Goetz R, Rosenfield P, Malaspina D. Family history of affective illness in schizophrenia patients: symptoms and cognition. Schizophr Res. 2009;110(1-3):24-7.

175. Ammari N, Heinrichs RW, Miles AA. An investigation of 3 neurocognitive subtypes in schizophrenia. Schizophr Res. 2010;121(1-3):32-8.

176. Bryson G, Bell M, Kaplan E, Greig T, Lysaker P. Affect recognition in deficit syndrome schizophrenia. Psychiatry research. 1998;77(2):113-20.

177. Earnst KS, Kring AM. Emotional responding in deficit and non-deficit schizophrenia. Psychiatry research. 1999;88(3):191-207.

178. Fahim C, Stip E, Mancini-Marie A, Gendron A, Mensour B, Beauregard M. Differential hemodynamic brain activity in schizophrenia patients with blunted affect during quetiapine treatment. Journal of clinical psychopharmacology. 2005;25(4):367-71.

179. Fahim C, Stip E, Mancini-Marie A, Mensour B, Boulay LJ, Leroux JM, et al. Brain activity during emotionally negative pictures in schizophrenia with and without flat affect: an fMRI study. Psychiatry Res. 2005;140(1):1-15.

180. Mancini-Marie A, Stip E, Fahim C, Mensour B, Leroux JM, Beaudoin G, et al. Fusiform gyrus and possible impairment of the recognition of emotional expression in schizophrenia subjects with blunted affect: a fMRI preliminary report. Brain and cognition. 2004;54(2):153-5.

181. Cohen AS, Docherty NM. Deficit versus negative syndrome in schizophrenia: prediction of attentional impairment. Schizophr Bull. 2004;30(4):827-35.

182. Farkas M. [Psychopathologic and cognitive investigations in schizophrenia]. Orvosi hetilap. 2009;150(9):423-9.

183. Morrison RL, Bellack AS, Mueser KT. Deficits in facial-affect recognition and schizophrenia. Schizophr Bull. 1988;14(1):67-83.

184. Strauss ME. Behavioral differences between acute and chronic schizophrenics: course of psychosis, effects of institutionalization, or sampling biases? Psychological bulletin. 1973;79(5):271-9.

185. Pogue-Geile MF, Harrow M. Negative symptoms in schizophrenia: their longitudinal course and prognostic importance. Schizophr Bull. 1985;11(3):427-39.

186. Breier A, Schreiber JL, Dyer J, Pickar D. National Institute of Mental Health longitudinal study of chronic schizophrenia. Prognosis and predictors of outcome. Arch Gen Psychiatry. 1991;48(3):239-46.

187. Grimes K, Walker EF. Childhood emotional expressions, educational attainment, and age at onset of illness in schizophrenia. Journal of abnormal psychology. 1994;103(4):784-90.

188. Corcoran R, Mercer G, Frith CD. Schizophrenia, symptomatology and social inference: investigating "theory of mind" in people with schizophrenia. Schizophr Res. 1995;17(1):5-13.

189. Postmes L, Sno HN, Goedhart S, van der Stel J, Heering HD, de Haan L. Schizophrenia as a self-disorder due to perceptual incoherence. Schizophr Res. 2014;152(1):41-50.

190. Borda J, Sass L. Phenomenology and neurobiology of self disorder in schizophrenia: Primary factors. Schizophr Res. 2015;(In press).

191. Pettersson-Yeo W, Allen P, Benetti S, McGuire P, Mechelli A. Dysconnectivity in schizophrenia: where are we now? Neurosci Biobehav Rev. 2011;35(5):1110-24.

192. Schmitt A, Hasan A, Gruber O, Falkai P. Schizophrenia as a disorder of disconnectivity. European archives of psychiatry and clinical neuroscience. 2011;261 Suppl 2:S150-4.

193. Gavrilescu M, Rossell S, Stuart GW, Shea TL, Innes-Brown H, Henshall K, et al. Reduced connectivity of the auditory cortex in patients with auditory hallucinations: a resting state functional magnetic resonance imaging study. Psychological medicine. 2010;40(7):1149-58.

194. Vercammen A, Knegtering H, Liemburg EJ, den Boer JA, Aleman A. Functional connectivity of the temporo-parietal region in schizophrenia: effects of rTMS treatment of auditory hallucinations. Journal of psychiatric research. 2010;44(11):725-31.

195. Fornito A, Bullmore ET. Reconciling abnormalities of brain network structure and function in schizophrenia. Current opinion in neurobiology. 2014;30C:44-50.

196. Goldman MB. Brain circuit dysfunction in a distinct subset of chronic psychotic patients. Schizophrenia research. 2014;157(1-3):204-13.

197. van den Heuvel MP, Fornito A. Brain networks in schizophrenia. Neuropsychol Rev. 2014;24(1):32-48.

198. McGlashan TH, Hoffman RE. Schizophrenia as a disorder of developmentally reduced synaptic connectivity. Arch Gen Psychiatry. 2000;57(7):637-48.

199. Woo TU. Neurobiology of schizophrenia onset. Current topics in behavioral neurosciences. 2014;16:267-95.

200. Jones EG. Cortical development and neuropathology in schizophrenia. Ciba Found Symp. 1995;193:277-95.

201. Jones EG. Cortical development and thalamic pathology in schizophrenia. Schizophr Bull. 1997;23(3):483-501.

202. Selemon LD, Goldman-Rakic PS. The reduced neuropil hypothesis: a circuit based model of schizophrenia. Biol Psychiatry. 1999;45(1):17-25.

203. Andreasen NC, Paradiso S, O'Leary DS. "Cognitive dysmetria" as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? Schizophr Bull. 1998;24(2):203-18.

204. Buckley PF, Pillai A, Evans D, Stirewalt E, Mahadik S. Brain derived neurotropic factor in first-episode psychosis. Schizophr Res. 2007;91(1-3):1-5.

205. McGrath J. Dissecting the heterogeneity of schizophrenia outcomes. Schizophr Bull. 2008;34(2):247-8.

206. Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, "just the facts" 5. Treatment and prevention. Past, present, and future. Schizophr Res. 2010;122(1-3):1-23.

207. Harrow M, Grossman LS, Jobe TH, Herbener ES. Do patients with schizophrenia ever show periods of recovery? A 15-year multi-follow-up study. Schizophr Bull. 2005;31(3):723-34.

208. Harrow M, Jobe TH. Longitudinal studies of outcome and recovery in schizophrenia and early intervention: can they make a difference? Canadian journal of psychiatry Revue canadienne de psychiatrie. 2005;50(14):879-80.

209. Jobe TH, Harrow M. Long-term outcome of patients with schizophrenia: a review. Canadian journal of psychiatry Revue canadienne de psychiatrie. 2005;50(14):892-900.

210. Macleod SH, Elliott L, Brown R. What support can community mental health nurses deliver to carers of people diagnosed with schizophrenia? Findings from a review of the literature. International journal of nursing studies. 2011;48(1):100-20.

211. Suttajit S, Srisurapanont M, Xia J, Maneeton B, Maneeton N. Quetiapine versus typical antipsychotic medications for schizophrenia. The Cochrane database of systematic reviews. 2013;5:CD007815.

212. Kishimoto T, Agarwal V, Kishi T, Leucht S, Kane JM, Correll CU. Relapse prevention in schizophrenia: a systematic review and meta-analysis of second-generation antipsychotics versus first-generation antipsychotics. Molecular psychiatry. 2013;18(1):53-66.

213. Miyamoto S, Duncan GE, Marx CE, Lieberman JA. Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. Molecular psychiatry. 2005;10(1):79-104.

214. Fleischhacker WW. New drugs for the treatment of schizophrenic patients. Acta psychiatrica Scandinavica Supplementum. 1995;388:24-30.

215. Hawkins KA, Mohamed S, Woods SW. Will the novel antipsychotics significantly ameliorate neuropsychological deficits and improve adaptive functioning in schizophrenia? Psychol Med. 1999;29(1):1-8.

216. Desamericq G, Schurhoff F, Meary A, Szoke A, Macquin-Mavier I, Bachoud-Levi AC, et al. Long-term neurocognitive effects of antipsychotics in schizophrenia: a network meta-analysis. Eur J Clin Pharmacol. 2014;70(2):127-34.

217. Faber G, van Gool AR, Smid HG, Wiersma D, van den Bosch RJ. [Typical and atypical antipsychotics: Is there a difference in their influence on neurocognition?]. Tijdschrift voor psychiatrie. 2011;53(2):107-17.

218. Hartling L, Abou-Setta AM, Dursun S, Mousavi SS, Pasichnyk D, Newton AS. Antipsychotics in adults with schizophrenia: comparative effectiveness of first-generation versus second-generation medications: a systematic review and meta-analysis. Annals of internal medicine. 2012;157(7):498-511.

219. Keefe RS, Sweeney JA, Gu H, Hamer RM, Perkins DO, McEvoy JP, et al. Effects of olanzapine, quetiapine, and risperidone on neurocognitive function in early psychosis: a randomized, double-blind 52-week comparison. The American journal of psychiatry. 2007;164(7):1061-71.

220. Remington G, Kapur S. Atypical antipsychotics: are some more atypical than others? Psychopharmacology. 2000;148(1):3-15.

221. Tandon R. Antipsychotics in the treatment of schizophrenia: an overview. The Journal of clinical psychiatry. 2011;72 Suppl 1:4-8.

222. Taylor D. Atypical antipsychotics not associated with improved hospitalisation outcomes compared with typical antipsychotics in people with schizophrenia in real practice. Evidence-based mental health. 2013;16(2):36.

223. Shen WW. A history of antipsychotic drug development. Compr Psychiatry. 1999;40(6):407-14.

224. Lopez-Munoz F, Alamo C, Cuenca E, Shen WW, Clervoy P, Rubio G. History of the discovery and clinical introduction of chlorpromazine. Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists. 2005;17(3):113-35.

225. Stip E. Happy birthday neuroleptics! 50 years later: la folie du doute. Eur Psychiatry. 2002;17(3):115-9.

226. Keefe RS, Silva SG, Perkins DO, Lieberman JA. The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: a review and meta-analysis. Schizophr Bull. 1999;25(2):201-22.

227. Meltzer HY, McGurk SR. The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. Schizophr Bull. 1999;25(2):233-55.

228. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. The New England journal of medicine. 2005;353(12):1209-23.

229. Jones PB, Barnes TR, Davies L, Dunn G, Lloyd H, Hayhurst KP, et al. Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry. 2006;63(10):1079-87.

230. Swartz MS, Stroup TS, McEvoy JP, Davis SM, Rosenheck RA, Keefe RS, et al. What CATIE found: results from the schizophrenia trial. Psychiatric services. 2008;59(5):500-6.

231. Swartz MS, Wagner HR, Swanson JW, Stroup TS, McEvoy JP, Reimherr F, et al. The effectiveness of antipsychotic medications in patients who use or avoid illicit substances: results from the CATIE study. Schizophr Res. 2008;100(1-3):39-52.

232. Xia J, Merinder LB, Belgamwar MR. Psychoeducation for schizophrenia. Schizophr Bull. 2011;37(1):21-2.

233. Sin J, Norman I. Psychoeducational interventions for family members of people with schizophrenia: a mixed-method systematic review. J Clin Psychiatry. 2013;74(12):e1145-62.

234. Pitschel-Walz G, Leucht S, Bauml J, Kissling W, Engel RR. The effect of family interventions on relapse and rehospitalization in schizophrenia--a meta-analysis. Schizophr Bull. 2001;27(1):73-92.

235. Hode Y. [Psychoeducation of patients and their family members during episode psychosis]. Encephale. 2013;39 Suppl 2:S110-4.

236. Giron M, Fernandez-Yanez A, Mana-Alvarenga S, Molina-Habas A, Nolasco A, Gomez-Beneyto M. Efficacy and effectiveness of individual family intervention on social and clinical functioning and family burden in severe schizophrenia: a 2-year randomized controlled study. Psychol Med. 2010;40(1):73-84.

237. Keshavan MS, Vinogradov S, Rumsey J, Sherrill J, Wagner A. Cognitive training in mental disorders: update and future directions. Am J Psychiatry. 2014;171(5):510-22.

238. Velligan DI, Tai S, Roberts DL, Maples-Aguilar N, Brown M, Mintz J, et al. A Randomized Controlled Trial Comparing Cognitive Behavior Therapy, Cognitive Adaptation Training, Their Combination and Treatment as Usual in Chronic Schizophrenia. Schizophr Bull. 2014.

239. Elis O, Caponigro JM, Kring AM. Psychosocial treatments for negative symptoms in schizophrenia: current practices and future directions. Clin Psychol Rev. 2013;33(8):914-28.

240. Kurtz MM, Mueser KT. A meta-analysis of controlled research on social skills training for schizophrenia. J Consult Clin Psychol. 2008;76(3):491-504.

241. Gould RA, Mueser KT, Bolton E, Mays V, Goff D. Cognitive therapy for psychosis in schizophrenia: an effect size analysis. Schizophr Res. 2001;48(2-3):335-42.

242. Zimmermann G, Favrod J, Trieu VH, Pomini V. The effect of cognitive behavioral treatment on the positive symptoms of schizophrenia spectrum disorders: a meta-analysis. Schizophr Res. 2005;77(1):1-9.

243. Morrison AP, Pyle M, Chapman N, French P, Parker SK, Wells A. Metacognitive therapy in people with a schizophrenia spectrum diagnosis and medication resistant symptoms: a feasibility study. J Behav Ther Exp Psychiatry. 2014;45(2):280-4.

244. Morrison AP, Turkington D, Pyle M, Spencer H, Brabban A, Dunn G, et al. Cognitive therapy for people with schizophrenia spectrum disorders not taking antipsychotic drugs: a single-blind randomised controlled trial. Lancet. 2014;383(9926):1395-403.

245. Thase ME, Kingdon D, Turkington D. The promise of cognitive behavior therapy for treatment of severe mental disorders: a review of recent developments. World Psychiatry. 2014;13(3):244-50.

246. McGurk SR, Mueser KT, Feldman K, Wolfe R, Pascaris A. Cognitive training for supported employment: 2-3 year outcomes of a randomized controlled trial. The American journal of psychiatry. 2007;164(3):437-41.

247. McGurk SR, Twamley EW, Sitzer DI, McHugo GJ, Mueser KT. A meta-analysis of cognitive remediation in schizophrenia. The American journal of psychiatry. 2007;164(12):1791-802.

248. Pillet B, Morvan Y, Todd A, Franck N, Duboc C, Grosz A, et al. Cognitive remediation therapy (CRT) benefits more to patients with schizophrenia with low initial memory performances. Disabil Rehabil. 2015;37(10):846-53.

249. Keefe RS, Haig GM, Marder SR, Harvey PD, Dunayevich E, Medalia A, et al. Report on ISCTM Consensus Meeting on Clinical Assessment of Response to Treatment of Cognitive Impairment in Schizophrenia. Schizophr Bull. 2016;42(1):19-33.

250. Isaac C, Januel D. Neural correlates of cognitive improvements following cognitive remediation in schizophrenia: a systematic review of randomized trials. Socioaffect Neurosci Psychol. 2016;6:30054.

251. Wei YY, Wang JJ, Yan C, Li ZQ, Pan X, Cui Y, et al. Correlation Between Brain Activation Changes and Cognitive Improvement Following Cognitive Remediation Therapy in Schizophrenia: An Activation Likelihood Estimation Meta-analysis. Chin Med J (Engl). 2016;129(5):578-85.

252. Hazell CM, Hayward M, Cavanagh K, Strauss C. A systematic review and meta-analysis of low intensity CBT for psychosis. Clin Psychol Rev. 2016;45:183-92.

253. Matsuda Y, Morimoto T, Furukawa S, Sato S, Hatsuse N, Iwata K, et al. Feasibility and effectiveness of a cognitive remediation programme with original computerised cognitive training and group intervention for schizophrenia: a multicentre randomised trial. Neuropsychol Rehabil. 2016:1-11.

254. Kurtz MM, Richardson CL. Social cognitive training for schizophrenia: a meta-analytic investigation of controlled research. Schizophr Bull. 2012;38(5):1092-104.

255. Wykes T, Steel C, Everitt B, Tarrier N. Cognitive behavior therapy for schizophrenia: effect sizes, clinical models, and methodological rigor. Schizophr Bull. 2008;34(3):523-37.

256. Kumari V, Fannon D, Peters ER, Ffytche DH, Sumich AL, Premkumar P, et al. Neural changes following cognitive behaviour therapy for psychosis: a longitudinal study. Brain. 2011;134(Pt 8):2396-407.

257. Wood L, Byrne R, Varese F, Morrison AP. Psychosocial interventions for internalised stigma in people with a schizophrenia-spectrum diagnosis: A systematic narrative synthesis and meta-analysis. Schizophr Res. 2016.

258. Matsui M, Arai H, Yonezawa M, Sumiyoshi T, Suzuki M, Kurachi M. The effects of cognitive rehabilitation on social knowledge in patients with schizophrenia. Applied neuropsychology. 2009;16(3):158-64.

259. Medalia A, Opler LA, Saperstein AM. Integrating psychopharmacology and cognitive remediation to treat cognitive dysfunction in the psychotic disorders. CNS spectrums. 2014;19(2):115-20.

260. Meisenzahl EM, Koutsouleris N, Bottlender R, Scheuerecker J, Jager M, Teipel SJ, et al. Structural brain alterations at different stages of schizophrenia: a voxel-based morphometric study. Schizophr Res. 2008;104(1-3):44-60.

261. Sun D, Phillips L, Velakoulis D, Yung A, McGorry PD, Wood SJ, et al. Progressive brain structural changes mapped as psychosis develops in 'at risk' individuals. Schizophr Res. 2009;108(1-3):85-92.

262. Steen RG, Mull C, McClure R, Hamer RM, Lieberman JA. Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. Br J Psychiatry. 2006;188:510-8.

263. Lang DJ, Khorram B, Goghari VM, Kopala LC, Vandorpe RA, Rui Q, et al. Reduced anterior internal capsule and thalamic volumes in first-episode psychosis. Schizophr Res. 2006;87(1-3):89-99.

264. Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Mol Psychiatry. 2005;10(1):40-68; image 5.

265. Andreasen NC. A unitary model of schizophrenia: Bleuler's "fragmented phrene" as schizencephaly. Archives of general psychiatry. 1999;56(9):781-7.

266. Andreasen NC. Understanding the causes of schizophrenia. The New England journal of medicine. 1999;340(8):645-7.

267. van Os J, Kapur S. Schizophrenia. Lancet. 2009;374(9690):635-45.

268. Insel TR. Rethinking schizophrenia. Nature. 2010;468(7321):187-93.

269. Friston KJ, Frith CD. Schizophrenia: a disconnection syndrome? Clin Neurosci. 1995;3(2):89-97.

270. Sepede G, Spano MC, Lorusso M, De Berardis D, Salerno RM, Di Giannantonio M, et al. Sustained attention in psychosis: Neuroimaging findings. World journal of radiology. 2014;6(6):261-73.

271. Bora E, Fornito A, Radua J, Walterfang M, Seal M, Wood SJ, et al. Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis. Schizophr Res. 2011;127(1-3):46-57.

272. Wolf RC, Hose A, Frasch K, Walter H, Vasic N. Volumetric abnormalities associated with cognitive deficits in patients with schizophrenia. Eur Psychiatry. 2008;23(8):541-8.

273. Lui S, Deng W, Huang X, Jiang L, Ma X, Chen H, et al. Association of cerebral deficits with clinical symptoms in antipsychotic-naive first-episode schizophrenia: an optimized voxel-based morphometry and resting state functional connectivity study. The American journal of psychiatry. 2009;166(2):196-205.

274. Yamada M, Hirao K, Namiki C, Hanakawa T, Fukuyama H, Hayashi T, et al. Social cognition and frontal lobe pathology in schizophrenia: a voxel-based morphometric study. Neuroimage. 2007;35(1):292-8.

275. Honea R, Crow TJ, Passingham D, Mackay CE. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. The American journal of psychiatry. 2005;162(12):2233-45.

276. Neckelmann G, Specht K, Lund A, Ersland L, Smievoll AI, Neckelmann D, et al. Mr morphometry analysis of grey matter volume reduction in schizophrenia: association with hallucinations. Int J Neurosci. 2006;116(1):9-23.

277. Giuliani NR, Calhoun VD, Pearlson GD, Francis A, Buchanan RW. Voxel-based morphometry versus region of interest: a comparison of two methods for analyzing gray matter differences in schizophrenia. Schizophr Res. 2005;74(2-3):135-47.

278. Salgado-Pineda P, Junque C, Vendrell P, Baeza I, Bargallo N, Falcon C, et al. Decreased cerebral activation during CPT performance: structural and functional deficits in schizophrenic patients. Neuroimage. 2004;21(3):840-7.

279. Kubicki M, Shenton ME, Salisbury DF, Hirayasu Y, Kasai K, Kikinis R, et al. Voxel-based morphometric analysis of gray matter in first episode schizophrenia. Neuroimage. 2002;17(4):1711-9.

280. Hulshoff Pol HE, Schnack HG, Mandl RC, van Haren NE, Koning H, Collins DL, et al. Focal gray matter density changes in schizophrenia. Arch Gen Psychiatry. 2001;58(12):1118-25.

281. Lewine R. At issue: Sex and gender in schizophrenia. Schizophr Bull. 2004;30(4):755-62.

282. Lewine R, Haden C, Caudle J, Shurett R. Sex-onset effects on neuropsychological function in schizophrenia. Schizophr Bull. 1997;23(1):51-61.

283. Lewine RR. Sex differences in age of symptom onset and first hospitalization in schizophrenia. The American journal of orthopsychiatry. 1980;50(2):316-22.

284. Lewine RR, Thurston-Snoha BJ, Ardery R. Sex, gender, and neuropsychological functioning in schizophrenia. Journal of clinical and experimental neuropsychology. 2006;28(8):1362-72.

285. Lewine RR, Walker EF, Shurett R, Caudle J, Haden C. Sex differences in neuropsychological functioning among schizophrenic patients. The American journal of psychiatry. 1996;153(9):1178-84.

286. van der Werf M, Hanssen M, Kohler S, Verkaaik M, Verhey FR, van Winkel R, et al. Systematic review and collaborative recalculation of 133,693 incident cases of schizophrenia. Psychol Med. 2014;44(1):9-16.

287. McGrath JJ, Susser ES. New directions in the epidemiology of schizophrenia. The Medical journal of Australia. 2009;190(4 Suppl):S7-9.

288. Okkels N, Vernal DL, Jensen SO, McGrath JJ, Nielsen RE. Changes in the diagnosed incidence of early onset schizophrenia over four decades. Acta psychiatrica Scandinavica. 2013;127(1):62-8.

289. Anderson KK. Health service registry data in psychiatric epidemiology: challenges for definition and interpretation: an editorial comment to: Okkels et al.'s 'changes in the diagnosed incidence of early onset schizophrenia over four decades' (1). Acta psychiatrica Scandinavica. 2013;127(1):9-10.

290. Vanasse A, Courteau J, Fleury MJ, Gregoire JP, Lesage A, Moisan J. Treatment prevalence and incidence of schizophrenia in Quebec using a population health services perspective: different algorithms, different estimates. Social psychiatry and psychiatric epidemiology. 2012;47(4):533-43.

291. Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. PLoS Med. 2005;2(5):e141.

292. Abel KM, Drake R, Goldstein JM. Sex differences in schizophrenia. International review of psychiatry. 2010;22(5):417-28.

293. Perala J, Suvisaari J, Saarni SI, Kuoppasalmi K, Isometsa E, Pirkola S, et al. Lifetime prevalence of psychotic and bipolar I disorders in a general population. Arch Gen Psychiatry. 2007;64(1):19-28.

294. Hambrecht M, Riecher-Rossler A, Fatkenheuer B, Louza MR, Hafner H. Higher morbidity risk for schizophrenia in males: fact or fiction? Compr Psychiatry. 1994;35(1):39-49.

295. Leventhal DB, Schuck JR, Rothstein H. Gender differences in schizophrenia. J Nerv Ment Dis. 1984;172(8):464-7.

296. Angermeyer MC, Kuhn L. Gender differences in age at onset of schizophrenia. An overview. Eur Arch Psychiatry Neurol Sci. 1988;237(6):351-64.

297. Jayaswal SK, Adityanjee, Khandelwal SK. Age of onset of schizophrenia. The British journal of psychiatry : the journal of mental science. 1988;152:428.

298. Franzek E, Beckmann H. Sex differences and distinct subgroups in schizophrenia. A study of 54 chronic hospitalized schizophrenics. Psychopathology. 1992;25(2):90-9.

299. Hafner H, an der Heiden W, Behrens S, Gattaz WF, Hambrecht M, Loffler W, et al. Causes and consequences of the gender difference in age at onset of schizophrenia. Schizophr Bull. 1998;24(1):99-113.

300. Hafner H, Maurer K, Loffler W, an der Heiden W, Munk-Jorgensen P, Hambrecht M, et al. The ABC Schizophrenia Study: a preliminary overview of the results. Social psychiatry and psychiatric epidemiology. 1998;33(8):380-6.

301. Leung A, Chue P. Sex differences in schizophrenia, a review of the literature. Acta psychiatrica Scandinavica Supplementum. 2000;401:3-38.

302. Hafner H, Fatkenheuer B, an der Heiden W, Loffler W, Maurer K, Munk-Jorgensen P, et al. [Sex differences in age of onset, symptomatology and evolution of schizophrenia]. Sante mentale au Quebec. 1991;16(1):77-98.

303. Salem JE, Kring AM. The role of gender differences in the reduction of etiologic heterogeneity in schizophrenia. Clin Psychol Rev. 1998;18(7):795-819.

304. Voronkov BV. [Relationship between sex and the clinical picture of schizophrenia in adolescents]. Zhurnal nevropatologii i psikhiatrii imeni SS Korsakova. 1978;78(10):1528-31.

305. Shimizu A, Kurachi M, Noda M, Yamaguchi N, Torii H, Isaki K. Influence of sex on age at onset of schizophrenia. The Japanese journal of psychiatry and neurology. 1988;42(1):35-40.

306. Gold DD, Jr. Late age of Onset Schizophrenia: present but unaccounted for. Compr Psychiatry. 1984;25(2):225-37.

307. Loranger AW. Sex difference in age at onset of schizophrenia. Arch Gen Psychiatry. 1984;41(2):157-61.

308. Meesters PD, de Haan L, Comijs HC, Stek ML, Smeets-Janssen MM, Weeda MR, et al. Schizophrenia spectrum disorders in later life: prevalence and distribution of age at onset and sex in a dutch catchment area. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2012;20(1):18-28.

309. Hafner H, Maurer K, Loffler W, Riecher-Rossler A. The influence of age and sex on the onset and early course of schizophrenia. The British journal of psychiatry : the journal of mental science. 1993;162:80-6.

310. Hafner H, Riecher-Rossler A, An Der Heiden W, Maurer K, Fatkenheuer B, Loffler W. Generating and testing a causal explanation of the gender difference in age at first onset of schizophrenia. Psychol Med. 1993;23(4):925-40.

311. Hafner H, Hambrecht M, Loffler W, Munk-Jorgensen P, Riecher-Rossler A. Is schizophrenia a disorder of all ages? A comparison of first episodes and early course across the life-cycle. Psychol Med. 1998;28(2):351-65.

312. Hafner H, Riecher-Rossler A, Maurer K, Fatkenheuer B, Loffler W. First onset and early symptomatology of schizophrenia. A chapter of epidemiological and neurobiological research into age and sex differences. European archives of psychiatry and clinical neuroscience. 1992;242(2-3):109-18.

313. Larsen TK, McGlashan TH, Johannessen JO, Vibe-Hansen L. First-episode schizophrenia: II. Premorbid patterns by gender. Schizophr Bull. 1996;22(2):257-69.

314. Albus M, Scherer J, Hueber S, Lechleuthner T, Kraus G, Zausinger S, et al. The impact of familial loading on gender differences in age at onset of schizophrenia. Acta psychiatrica Scandinavica. 1994;89(2):132-4.

315. Riecher-Rossler A, Hafner H, Dutsch-Strobel A, Oster M, Stumbaum M, van Gulick-Bailer M, et al. Further evidence for a specific role of estradiol in schizophrenia? Biol Psychiatry. 1994;36(7):492-4.

316. Folnegovic Z, Folnegovic-Smalc V. Schizophrenia in Croatia: age of onset differences between males and females. Schizophr Res. 1994;14(1):83-91.

317. Baron M, Gruen R, Asnis L, Kane J. Age-of-onset in schizophrenia and schizotypal disorders. Clinical and genetic implications. Neuropsychobiology. 1983;10(4):199-204.

318. Murthy GV, Janakiramaiah N, Gangadhar BN, Subbakrishna DK. Sex difference in age at onset of schizophrenia: discrepant findings from India. Acta psychiatrica Scandinavica. 1998;97(5):321-5.

319. Venkatesh BK, Thirthalli J, Naveen MN, Kishorekumar KV, Arunachala U, Venkatasubramanian G, et al. Sex difference in age of onset of schizophrenia: findings from a community-based study in India. World Psychiatry. 2008;7(3):173-6.

320. DeLisi LE, Bass N, Boccio A, Shields G, Morganti C. Age of onset in familial schizophrenia. Arch Gen Psychiatry. 1994;51(4):334-5.

321. Gorwood P, Leboyer M, Jay M, Payan C, Feingold J. Gender and age at onset in schizophrenia: impact of family history. The American journal of psychiatry. 1995;152(2):208-12.
322. Bromet EJ, Schwartz JE, Fennig S, Geller L, Jandorf L, Kovasznay B, et al. The epidemiology of psychosis: the Suffolk County Mental Health Project. Schizophr Bull. 1992;18(2):243-55.
323. Lewine R. Schizophrenia: an amotivational syndrome in men. Canadian journal of psychiatry Revue canadienne de psychiatrie. 1985;30(5):316-8.
324. Nasser EH, Walders N, Jenkins JH. The experience of schizophrenia: what's gender got to do with it? A critical review of the current status of research on schizophrenia. Schizophr Bull. 2002;28(2):351-62.
325. Hafner H. Gender differences in schizophrenia. Psychoneuroendocrinology. 2003;28 Suppl 2:17-54.
326. Haas GL, Glick ID, Clarkin JF, Spencer JH, Lewis AB. Gender and schizophrenia outcome: a clinical trial of an inpatient family intervention. Schizophr Bull. 1990;16(2):277-92.
327. Bardenstein KK, McGlashan TH. Gender differences in affective, schizoaffective, and schizophrenic disorders. A review. Schizophr Res. 1990;3(3):159-72.
328. Castle DJ, Wessely S, Murray RM. Sex and schizophrenia: effects of diagnostic stringency, and associations with and premorbid variables. The British journal of psychiatry : the journal of mental science. 1993;162:658-64.
329. Childers SE, Harding CM. Gender, premorbid social functioning, and long-term outcome in DSM-III schizophrenia. Schizophr Bull. 1990;16(2):309-18.
330. Goldstein JM, Tsuang MT, Faraone SV. Gender and schizophrenia: implications for understanding the heterogeneity of the illness. Psychiatry research. 1989;28(3):243-53.
331. McGlashan TH, Bardenstein KK. Gender differences in affective, schizoaffective, and schizophrenic disorders. Schizophr Bull. 1990;16(2):319-29.
332. Monte RC, Goulding SM, Compton MT. Premorbid functioning of patients with first-episode nonaffective psychosis: a comparison of deterioration in academic and social performance, and clinical correlates of Premorbid Adjustment Scale scores. Schizophr Res. 2008;104(1-3):206-13.

333. Mueser KT, Bellack AS, Morrison RL, Wade JH. Gender, social competence, and symptomatology in schizophrenia: a longitudinal analysis. Journal of abnormal psychology. 1990;99(2):138-47.

334. Weiser M, Reichenberg A, Rabinowitz J, Kaplan Z, Mark M, Nahon D, et al. Gender differences in premorbid cognitive performance in a national cohort of schizophrenic patients. Schizophr Res. 2000;45(3):185-90.

335. Crow TJ. Brain changes and negative symptoms in schizophrenia. Psychopathology. 1995;28(1):18-21.

336. Willhite RK, Niendam TA, Bearden CE, Zinberg J, O'Brien MP, Cannon TD. Gender differences in symptoms, functioning and social support in patients at ultra-high risk for developing a psychotic disorder. Schizophr Res. 2008;104(1-3):237-45.

337. Strauss GP, Allen DN, Miski P, Buchanan RW, Kirkpatrick B, Carpenter WT, Jr. Differential patterns of premorbid social and academic deterioration in deficit and nondeficit schizophrenia. Schizophr Res. 2012;135(1-3):134-8.

338. Chang WC, Hui CL, Tang JY, Wong GH, Lam MM, Chan SK, et al. Persistent negative symptoms in first-episode schizophrenia: a prospective three-year follow-up study. Schizophr Res. 2011;133(1-3):22-8.

339. Allen DN, Strauss GP, Barchard KA, Vertinski M, Carpenter WT, Buchanan RW. Differences in developmental changes in academic and social premorbid adjustment between males and females with schizophrenia. Schizophr Res. 2013;146(1-3):132-7.

340. Kulkarni J, Gavrilidis E, Hayes E, Heaton V, Worsley R. Special biological issues in the management of women with schizophrenia. Expert Rev Neurother. 2012;12(7):823-33.

341. Kulkarni J, Hayes E, Gavrilidis E. Hormones and schizophrenia. Curr Opin Psychiatry. 2012;25(2):89-95.

342. Kulkarni J, Gavrilidis E, Worsley R, Hayes E. Role of estrogen treatment in the management of schizophrenia. CNS drugs. 2012;26(7):549-57.

343. Plocka M, Rybakowski J. [Gender differences in schizophrenia]. Psychiatria polska. 1992;26(5):327-36.

344. Wieselgren IM, Lindstrom LH. A prospective 1-5 year outcome study in first-admitted and readmitted schizophrenic patients; relationship to heredity, premorbid adjustment, duration of

disease and education level at index admission and neuroleptic treatment. Acta psychiatrica Scandinavica. 1996;93(1):9-19.

345. Hafner H, Riecher A, Maurer K, Loffler W, Munk-Jorgensen P, Stromgren E. How does gender influence age at first hospitalization for schizophrenia? A transnational case register study. Psychol Med. 1989;19(4):903-18.

346. Malmberg A, Lewis G, David A, Allebeck P. Premorbid adjustment and personality in people with schizophrenia. The British journal of psychiatry : the journal of mental science. 1998;172:308-13; discussion 14-5.

347. Skokou M, Gourzis P. Demographic features and premorbid personality disorder traits in relation to age of onset and sex in paranoid schizophrenia. Psychiatry research. 2014;215(3):554-9.

348. Foerster A, Lewis S, Owen M, Murray R. Pre-morbid adjustment and personality in psychosis. Effects of sex and diagnosis. The British journal of psychiatry : the journal of mental science. 1991;158:171-6.

349. Addington J, Addington D. Premorbid functioning, cognitive functioning, symptoms and outcome in schizophrenia. J Psychiatry Neurosci. 1993;18(1):18-23.

350. Bailer J, Brauer W, Rey ER. Premorbid adjustment as predictor of outcome in schizophrenia: results of a prospective study. Acta psychiatrica Scandinavica. 1996;93(5):368-77.

351. Tamminga CA. Gender and schizophrenia. The Journal of clinical psychiatry. 1997;58 Suppl 15:33-7.

352. Schmael C, Georgi A, Krumm B, Buerger C, Deschner M, Nothen MM, et al. Premorbid adjustment in schizophrenia--an important aspect of phenotype definition. Schizophr Res. 2007;92(1-3):50-62.

353. Fennig S, Putnam K, Bromet EJ, Galambos N. Gender, premorbid characteristics and negative symptoms in schizophrenia. Acta psychiatrica Scandinavica. 1995;92(3):173-7.

354. O'Callaghan E, Buckley P, Redmond O, Stack J, Ennis JT, Larkin C, et al. Abnormalities of cerebral structure in schizophrenia on magnetic resonance imaging: interpretation in relation to the neurodevelopmental hypothesis. J R Soc Med. 1992;85(4):227-31.

355. Byrne M, Browne R, Mulryan N, Scully A, Morris M, Kinsella A, et al. Labour and delivery complications and schizophrenia. Case-control study using contemporaneous labour ward records. The British journal of psychiatry : the journal of mental science. 2000;176:531-6.

356. Preti A, Cardascia L, Zen T, Marchetti M, Favaretto G, Miotto P. Risk for obstetric complications and schizophrenia. Psychiatry research. 2000;96(2):127-39.

357. Dassa D, Azorin JM, Ledoray V, Sambuc R, Giudicelli S. Season of birth and schizophrenia: sex difference. Prog Neuropsychopharmacol Biol Psychiatry. 1996;20(2):243-51.

358. Dalman C, Allebeck P, Cullberg J, Grunewald C, Koster M. Obstetric complications and the risk of schizophrenia: a longitudinal study of a national birth cohort. Arch Gen Psychiatry. 1999;56(3):234-40.

359. Kirov G, Jones PB, Harvey I, Lewis SW, Toone BK, Rifkin L, et al. Do obstetric complications cause the earlier age at onset in male than female schizophrenics? Schizophr Res. 1996;20(1-2):117-24.

360. Lewis S. Sex and schizophrenia: vive la difference. The British journal of psychiatry : the journal of mental science. 1992;161:445-50.

361. Lewis SW, Murray RM. Obstetric complications, neurodevelopmental deviance, and risk of schizophrenia. J Psychiatr Res. 1987;21(4):413-21.

362. Susser E, Hoek HW, Brown A. Neurodevelopmental disorders after prenatal famine: The story of the Dutch Famine Study. American journal of epidemiology. 1998;147(3):213-6.

363. Stromgren E. Changes in the incidence of schizophrenia? The British journal of psychiatry : the journal of mental science. 1987;150:1-7.

364. Dassa D, Sham PC, Van Os J, Abel K, Jones P, Murray RM. [Season of birth, obstetric complications and schizophrenia]. L'Encephale. 1996;22 Spec No 3:9-12.

365. Brown AS, Begg MD, Gravenstein S, Schaefer CA, Wyatt RJ, Bresnahan M, et al. Serologic evidence of prenatal influenza in the etiology of schizophrenia. Arch Gen Psychiatry. 2004;61(8):774-80.

366. Khandaker GM, Zimbron J, Lewis G, Jones PB. Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population-based studies. Psychol Med. 2013;43(2):239-57.

367. Wright P, Takei N, Rifkin L, Murray RM. Maternal influenza, obstetric complications, and schizophrenia. The American journal of psychiatry. 1995;152(12):1714-20.

368. Machon RA, Mednick SA, Schulsinger F. Seasonality, birth complications and schizophrenia in a high risk sample. The British journal of psychiatry : the journal of mental science. 1987;151:122-4.

369. Schwartz PJ. Season of birth in schizophrenia: a maternal-fetal chronobiological hypothesis. Medical hypotheses. 2011;76(6):785-93.

370. Takei N, O'Callaghan E, Sham PC, Glover G, Murray RM. Does prenatal influenza divert susceptible females from later affective psychosis to schizophrenia? Acta psychiatrica Scandinavica. 1993;88(5):328-36.

371. Fineberg AM, Ellman LM, Buka S, Yolken R, Cannon TD. Decreased birth weight in psychosis: influence of prenatal exposure to serologically determined influenza and hypoxia. Schizophr Bull. 2013;39(5):1037-44.

372. Kneeland RE, Fatemi SH. Viral infection, inflammation and schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2013;42:35-48.

373. Nahmias AJ, Nahmias SB, Danielsson D. The possible role of transplacentally-acquired antibodies to infectious agents, with molecular mimicry to nervous system sialic acid epitopes, as causes of neuromental disorders: prevention and vaccine implications. Clinical & developmental immunology. 2006;13(2-4):167-83.

374. McGrath J. Hypothesis: is low prenatal vitamin D a risk-modifying factor for schizophrenia? Schizophr Res. 1999;40(3):173-7.

375. Rantakallio P, Jones P, Moring J, Von Wendt L. Association between central nervous system infections during childhood and adult onset schizophrenia and other psychoses: a 28-year follow-up. International journal of epidemiology. 1997;26(4):837-43.

376. Takei N, Murray RM, Sham P, O'Callaghan E. Schizophrenia risk for women from in utero exposure to influenza. The American journal of psychiatry. 1995;152(1):150-1.

377. Takei N, Sham P, O'Callaghan E, Murray GK, Glover G, Murray RM. Prenatal exposure to influenza and the development of schizophrenia: is the effect confined to females? The American journal of psychiatry. 1994;151(1):117-9.

378. Castle DJ, Abel K, Takei N, Murray RM. Gender differences in schizophrenia: hormonal effect or subtypes? Schizophr Bull. 1995;21(1):1-12.

379. Zornberg GL, Buka SL, Tsuang MT. The problem of obstetrical complications and schizophrenia. Schizophr Bull. 2000;26(2):249-56.

380. LaTorre RA. The psychological assessment of gender identity and gender role in schizophrenia. Schizophr Bull. 1976;2(2):266-85.

381. Sajatovic M, Jenkins JH, Strauss ME, Butt ZA, Carpenter E. Gender identity and implications for recovery among men and women with schizophrenia. Psychiatric services. 2005;56(1):96-8.

382. Cheek FE. A Serendipitous Finding: Sex Roles and Schizophrenia. Journal of abnormal psychology. 1964;69:392-400.

383. McClelland DC, Watt NF. Sex-role alienation in schizophrenia. Journal of abnormal psychology. 1968;73(3):226-39.

384. Ecker J, Levine J, Zigler E. Impaired sex-role identification in schizophrenia expressed in the comprehension of humor stimuli. The Journal of psychology. 1973;83(1st Half):67-77.

385. Parrott B, Lewine R. Socioeconomic status of origin and the clinical expression of Schizophrenia. Schizophr Res. 2005;75(2-3):417-24.

386. Chaves AC, Seeman MV, Mari JJ, Maluf A. Schizophrenia: impact of positive symptoms on gender social role. Schizophr Res. 1993;11(1):41-5.

387. Vila-Rodriguez F, Ochoa S, Autonell J, Usall J, Haro JM. Complex interaction between symptoms, social factors, and gender in social functioning in a community-dwelling sample of schizophrenia. The Psychiatric quarterly. 2011;82(4):261-74.

388. Fenton WS, McGlashan TH. Natural history of schizophrenia subtypes. II. Positive and negative symptoms and long-term course. Arch Gen Psychiatry. 1991;48(11):978-86.

389. Andreasen NC, Flaum M, Swayze VW, 2nd, Tyrrell G, Arndt S. Positive and negative symptoms in schizophrenia. A critical reappraisal. Arch Gen Psychiatry. 1990;47(7):615-21.

390. Ring N, Tantam D, Montague L, Newby D, Black D, Morris J. Gender differences in the incidence of definite schizophrenia and atypical psychosis--focus on negative symptoms of schizophrenia. Acta Psychiatr Scand. 1991;84(6):489-96.

391. Kay SR, Opler LA, Fiszbein A. Significance of positive and negative syndromes in chronic schizophrenia. Br J Psychiatry. 1986;149:439-48.

392. Schultz SK, Miller DD, Oliver SE, Arndt S, Flaum M, Andreasen NC. The life course of schizophrenia: age and symptom dimensions. Schizophr Res. 1997;23(1):15-23.

393. Morgan VA, Castle DJ, Jablensky AV. Do women express and experience psychosis differently from men? Epidemiological evidence from the Australian National Study of Low Prevalence (Psychotic) Disorders. The Australian and New Zealand journal of psychiatry. 2008;42(1):74-82.

394. Roy MA, Maziade M, Labbe A, Merette C. Male gender is associated with deficit schizophrenia: a meta-analysis. Schizophr Res. 2001;47(2-3):141-7.

395. Chang WC, Hui CL, Tang JY, Wong GH, Chan SK, Lee EH, et al. Impacts of duration of untreated psychosis on cognition and negative symptoms in first-episode schizophrenia: a 3-year prospective follow-up study. Psychol Med. 2013;43(9):1883-93.

396. Choi JS, Chon MW, Kang DH, Jung MH, Kwon JS. Gender difference in the prodromal symptoms of first-episode schizophrenia. Journal of Korean medical science. 2009;24(6):1083-8.

397. Mayer C, Kelterborn G, Naber D. Age of onset in schizophrenia: relations to psychopathology and gender. The British journal of psychiatry : the journal of mental science. 1993;162:665-71.

398. Lindstrom E, von Knorring L. Symptoms in schizophrenic syndromes in relation to age, sex, duration of illness and number of previous hospitalizations. Acta psychiatrica Scandinavica. 1994;89(4):274-8.

399. Gur RE, Petty RG, Turetsky BI, Gur RC. Schizophrenia throughout life: sex differences in severity and profile of symptoms. Schizophr Res. 1996;21(1):1-12.

400. Kendler KS, Walsh D. Gender and schizophrenia. Results of an epidemiologically-based family study. The British journal of psychiatry : the journal of mental science. 1995;167(2):184-92.

401. Addington D, Addington J, Patten S. Gender and affect in schizophrenia. Canadian journal of psychiatry Revue canadienne de psychiatrie. 1996;41(5):265-8.

402. Lindamer LA, Lohr JB, Harris MJ, McAdams LA, Jeste DV. Gender-related clinical differences in older patients with schizophrenia. The Journal of clinical psychiatry. 1999;60(1):61-7; quiz 8-9.

403. Andia AM, Zisook S, Heaton RK, Hesselink J, Jernigan T, Kuck J, et al. Gender differences in schizophrenia. J Nerv Ment Dis. 1995;183(8):522-8.

404. Shtasel DL, Gur RE, Gallacher F, Heimberg C, Gur RC. Gender differences in the clinical expression of schizophrenia. Schizophr Res. 1992;7(3):225-31.

405. Szymanski S, Lieberman JA, Alvir JM, Mayerhoff D, Loebel A, Geisler S, et al. Gender differences in onset of illness, treatment response, course, and biologic indexes in first-episode schizophrenic patients. Am J Psychiatry. 1995;152(5):698-703.

406. Goldstein JM, Link BG. Gender and the expression of schizophrenia. J Psychiatr Res. 1988;22(2):141-55.

407. Marneros A. Frequency of occurrence of Schneider's first rank symptoms in Schizophrenia. Eur Arch Psychiatry Neurol Sci. 1984;234(1):78-82.

408. Rector NA, Seeman MV. Auditory hallucinations in women and men. Schizophr Res. 1992;7(3):233-6.

409. Hambrecht M, Maurer K, Hafner H. Gender differences in schizophrenia in three cultures. Results of the WHO collaborative study on psychiatric disability. Social psychiatry and psychiatric epidemiology. 1992;27(3):117-21.

410. Beratis S, Gabriel J, Hoidas S. Age at onset in subtypes of schizophrenic disorders. Schizophr Bull. 1994;20(2):287-96.

411. Salokangas RK, Honkonen T, Saarinen S. Women have later onset than men in schizophrenia--but only in its paranoid form. Results of the DSP project. Eur Psychiatry. 2003;18(6):274-81.

412. Mancevski B, Keilp J, Kurzon M, Berman RM, Ortakov V, Harkavy-Friedman J, et al. Lifelong course of positive and negative symptoms in chronically institutionalized patients with schizophrenia. Psychopathology. 2007;40(2):83-92.

413. Thornicroft G, Leese M, Tansella M, Howard L, Toulmin H, Herran A, et al. Gender differences in living with schizophrenia. A cross-sectional European multi-site study. Schizophr Res. 2002;57(2-3):191-200.

414. Grigoriadis S, Seeman MV. The role of estrogen in schizophrenia: implications for schizophrenia practice guidelines for women. Can J Psychiatry. 2002;47(5):437-42.

415. Seeman MV. The role of estrogen in schizophrenia. J Psychiatry Neurosci. 1996;21(2):123-7.

416. Seeman MV. Psychopathology in women and men: focus on female hormones. Am J Psychiatry. 1997;154(12):1641-7.

417. Seeman MV, Lang M. The role of estrogens in schizophrenia gender differences. Schizophr Bull. 1990;16(2):185-94.

418. Canuso CM, Goldstein JM, Green AI. The evaluation of women with schizophrenia. Psychopharmacology bulletin. 1998;34(3):271-7.

419. Riecher-Rossler A, Hafner H. Schizophrenia and oestrogens--is there an association? European archives of psychiatry and clinical neuroscience. 1993;242(6):323-8.

420. Hafner H, Behrens S, De Vry J, Gattaz WF. Oestradiol enhances the vulnerability threshold for schizophrenia in women by an early effect on dopaminergic neurotransmission. Evidence from an epidemiological study and from animal experiments. European archives of psychiatry and clinical neuroscience. 1991;241(1):65-8.

421. Hafner H, Behrens S, De Vry J, Gattaz WF. An animal model for the effects of estradiol on dopamine-mediated behavior: implications for sex differences in schizophrenia. Psychiatry research. 1991;38(2):125-34.

422. Ghafari E, Fararouie M, Shirazi HG, Farhangfar A, Ghaderi F, Mohammadi A. Combination of estrogen and antipsychotics in the treatment of women with chronic schizophrenia: a double-blind, randomized, placebo-controlled clinical trial. Clinical schizophrenia & related psychoses. 2013;6(4):172-6.

423. Begemann MJ, Dekker CF, van Lunenburg M, Sommer IE. Estrogen augmentation in schizophrenia: a quantitative review of current evidence. Schizophr Res. 2012;141(2-3):179-84.

424. Chang SS, Renshaw DC. Psychosis and pregnancy. Compr Ther. 1986;12(10):36-41.

425. Kendell RE, Chalmers JC, Platz C. Epidemiology of puerperal psychoses. Br J Psychiatry. 1987;150:662-73.

426. Bergemann N, Parzer P, Runnebaum B, Resch F, Mundt C. Estrogen, menstrual cycle phases, and psychopathology in women suffering from schizophrenia. Psychol Med. 2007;37(10):1427-36.

427. Gattaz WF, Vogel P, Riecher-Rossler A, Soddu G. Influence of the menstrual cycle phase on the therapeutic response in schizophrenia. Biol Psychiatry. 1994;36(2):137-9.

428. Hallonquist JD, Seeman MV, Lang M, Rector NA. Variation in symptom severity over the menstrual cycle of schizophrenics. Biol Psychiatry. 1993;33(3):207-9.

429. Hendrick V, Altshuler LL, Burt VK. Course of psychiatric disorders across the menstrual cycle. Harv Rev Psychiatry. 1996;4(4):200-7.

430. Lambert M, Schimmelmann BG, Naber D, Schacht A, Karow A, Wagner T, et al. Prediction of remission as a combination of symptomatic and functional remission and adequate subjective well-being in 2960 patients with schizophrenia. The Journal of clinical psychiatry. 2006;67(11):1690-7.

431. Lipkovich IA, Deberdt W, Csernansky JG, Buckley P, Peuskens J, Kollack-Walker S, et al. Defining "good" and "poor" outcomes in patients with schizophrenia or schizoaffective disorder: a multidimensional data-driven approach. Psychiatry research. 2009;170(2-3):161-7.

432. Schennach-Wolff R, Jager M, Seemuller F, Obermeier M, Messer T, Laux G, et al. Defining and predicting functional outcome in schizophrenia and schizophrenia spectrum disorders. Schizophr Res. 2009;113(2-3):210-7.

433. Goldstein JM. Gender differences in the course of schizophrenia. Am J Psychiatry. 1988;145(6):684-9.

434. Usall J, Araya S, Ochoa S, Busquets E, Gost A, Marquez M. Gender differences in a sample of schizophrenic outpatients. Compr Psychiatry. 2001;42(4):301-5.

435. Grossman LS, Harrow M, Rosen C, Faull R. Sex differences in outcome and recovery for schizophrenia and other psychotic and nonpsychotic disorders. Psychiatric services. 2006;57(6):844-50.

436. Angermeyer MC, Kuhn L, Goldstein JM. Gender and the course of schizophrenia: differences in treated outcomes. Schizophr Bull. 1990;16(2):293-307.

437. Salokangas RK, Stengard E. Gender and short-term outcome in schizophrenia. Schizophr Res. 1990;3(5-6):333-45.

438. Gureje O, Bamidele RW. Gender and schizophrenia: association of age at onset with antecedent, clinical and outcome features. The Australian and New Zealand journal of psychiatry. 1998;32(3):415-23.

439. Nyman AK. Nonregressive schizophrenia--a long-term comparative follow-up investigation. Acta psychiatrica Scandinavica. 1989;79(1):59-73.

440. Grossman LS, Harrow M, Rosen C, Faull R, Strauss GP. Sex differences in schizophrenia and other psychotic disorders: a 20-year longitudinal study of psychosis and recovery. Compr Psychiatry. 2008;49(6):523-9.

441. Gearon JS, Bellack AS. Sex differences in illness presentation, course, and level of functioning in substance-abusing schizophrenia patients. Schizophr Res. 2000;43(1):65-70.

442. Heila H, Isometsa ET, Henriksson MM, Heikkinen ME, Marttunen MJ, Lonnqvist JK. Suicide and schizophrenia: a nationwide psychological autopsy study on age- and sex-specific clinical characteristics of 92 suicide victims with schizophrenia. The American journal of psychiatry. 1997;154(9):1235-42.

443. Mortensen PB, Juel K. Mortality and causes of death in first admitted schizophrenic patients. The British journal of psychiatry : the journal of mental science. 1993;163:183-9.
444. Newman SC, Bland RC, Thompson AH. Long-term course and outcome in schizophrenia: a 34-year follow-up study in Alberta, Canada. Psychol Med. 2012;42(10):2137-43.
445. Clemmensen L, Vernal DL, Steinhausen HC. A systematic review of the long-term outcome of early onset schizophrenia. BMC Psychiatry. 2012;12:150.
446. Lang FU, Kosters M, Lang S, Becker T, Jager M. Psychopathological long-term outcome of schizophrenia -- a review. Acta psychiatrica Scandinavica. 2013;127(3):173-82.
447. Lindamer LA, Bailey A, Hawthorne W, Folsom DP, Gilmer TP, Garcia P, et al. Gender differences in characteristics and service use of public mental health patients with schizophrenia. Psychiatric services. 2003;54(10):1407-9.
448. Ruggiero G, Sergi I, Iachini T. Gender differences in remembering and inferring spatial distances. Memory. 2008;16(8):821-35.
449. Linn MC, Petersen AC. Emergence and characterization of sex differences in spatial ability: a meta-analysis. Child Dev. 1985;56(6):1479-98.
450. Voyer D, Voyer S, Bryden MP. Magnitude of sex differences in spatial abilities: a meta-analysis and consideration of critical variables. Psychol Bull. 1995;117(2):250-70.
451. Halari R, Sharma T, Hines M, Andrew C, Simmons A, Kumari V. Comparable fMRI activity with differential behavioural performance on mental rotation and overt verbal fluency tasks in healthy men and women. Exp Brain Res. 2006;169(1):1-14.
452. Viveros MP, Mendrek A, Paus T, Lopez-Rodriguez AB, Marco EM, Yehuda R, et al. A comparative, developmental, and clinical perspective of neurobehavioral sexual dimorphisms. Front Neurosci. 2012;6:84.
453. Zhang XY, Chen da C, Xiu MH, Yang FD, Haile CN, Kosten TA, et al. Gender differences in never-medicated first-episode schizophrenia and medicated chronic schizophrenia patients. The Journal of clinical psychiatry. 2012;73(7):1025-33.
454. Seidman LJ, Goldstein JM, Goodman JM, Koren D, Turner WM, Faraone SV, et al. Sex differences in olfactory identification and Wisconsin Card Sorting performance in schizophrenia: relationship to attention and verbal ability. Biol Psychiatry. 1997;42(2):104-15.

455. Goldstein JM, Seidman LJ, Goodman JM, Koren D, Lee H, Weintraub S, et al. Are there sex differences in neuropsychological functions among patients with schizophrenia? The American journal of psychiatry. 1998;155(10):1358-64.

456. Jimenez J, Mancini-Marie A, Mendrek A. The case for not combining men and women in neurocognitive studies for schizophrenia. Schizophr Res. 2009;108(1-3):293-4.

457. Heinrichs RW. The primacy of cognition in schizophrenia. The American psychologist. 2005;60(3):229-42.

458. Sota TL, Heinrichs RW. Sex differences in verbal memory in schizophrenia patients treated with "typical" neuroleptics. Schizophr Res. 2003;62(1-2):175-82.

459. Voglmaier MM, Seidman LJ, Niznikiewicz MA, Dickey CC, Shenton ME, McCarley RW. A comparative profile analysis of neuropsychological function in men and women with schizotypal personality disorder. Schizophr Res. 2005;74(1):43-9.

460. Vaskinn A, Sundet K, Simonsen C, Hellvin T, Melle I, Andreassen OA. Sex differences in neuropsychological performance and social functioning in schizophrenia and bipolar disorder. Neuropsychology. 2011;25(4):499-510.

461. Torniainen M, Suvisaari J, Partonen T, Castaneda AE, Kuha A, Perala J, et al. Sex differences in cognition among persons with schizophrenia and healthy first-degree relatives. Psychiatry research. 2011;188(1):7-12.

462. Han M, Huang XF, Chen da C, Xiu MH, Hui L, Liu H, et al. Gender differences in cognitive function of patients with chronic schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2012;39(2):358-63.

463. Brebion G, Villalta-Gil V, Autonell J, Cervilla J, Dolz M, Foix A, et al. Cognitive correlates of verbal memory and verbal fluency in schizophrenia, and differential effects of various clinical symptoms between male and female patients. Schizophr Res. 2013;147(1):81-5.

464. Albus M, Hubmann W, Mohr F, Scherer J, Sobizack N, Franz U, et al. Are there gender differences in neuropsychological performance in patients with first-episode schizophrenia? Schizophr Res. 1997;28(1):39-50.

465. Bozikas VP, Kosmidis MH, Peltekis A, Giannakou M, Nimatoudis I, Karavatos A, et al. Sex differences in neuropsychological functioning among schizophrenia patients. The Australian and New Zealand journal of psychiatry. 2010;44(4):333-41.

466. Gogos A, Joshua N, Rossell SL. Use of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) to investigate group and gender differences in schizophrenia and bipolar disorder. The Australian and New Zealand journal of psychiatry. 2010;44(3):220-9.

467. Goldberg TE, Gold JM, Torrey EF, Weinberger DR. Lack of sex differences in the neuropsychological performance of patients with schizophrenia. The American journal of psychiatry. 1995;152(6):883-8.

468. Gur RC, Ragland JD, Moberg PJ, Bilker WB, Kohler C, Siegel SJ, et al. Computerized neurocognitive scanning: II. The profile of schizophrenia. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2001;25(5):777-88.

469. Hoff AL, Wieneke M, Faustman WO, Horon R, Sakuma M, Blankfeld H, et al. Sex differences in neuropsychological functioning of first-episode and chronically ill schizophrenic patients. The American journal of psychiatry. 1998;155(10):1437-9.

470. Ragland JD, Gur RC, Raz J, Schroeder L, Kohler CG, Smith RJ, et al. Effect of schizophrenia on frontotemporal activity during word encoding and recognition: a PET cerebral blood flow study. The American journal of psychiatry. 2001;158(7):1114-25.

471. Shipman SL, Baker EK, Pearlson G, Astur RS. Absence of established sex differences in patients with schizophrenia on a two-dimensional object array task. Psychiatry research. 2009;166(2-3):158-65.

472. Glaser E, Mendrek A, Germain M, Lakis N, Lavoie ME. Sex differences in memory of emotional images: a behavioral and electrophysiological investigation. Int J Psychophysiol. 2012;85(1):17-26.

473. Lecardeur L, Mendrek A, Stip E. Sexual dimorphism of spatial working memory profiles in schizophrenia. Cogn Neuropsychiatry. 2010;15(4):397-405.

474. Jimenez J, Mancini-Marie A, Mendrek A. The case for not combining men and women in neurocognitive studies for schizophrenia. Schizophr Res. 2009;108(1-3):293-4.

475. Kozaki T, Yasukouchi A. Sex differences on components of mental rotation at different menstrual phases. Int J Neurosci. 2009;119(1):59-67.

476. Gootjes L, Bruggeling EC, Magnee T, Van Strien JW. Sex differences in the latency of the late event-related potential mental rotation effect. Neuroreport. 2008;19(3):349-53.

477. Peters M, Manning JT, Reimers S. The effects of sex, sexual orientation, and digit ratio (2D:4D) on mental rotation performance. Arch Sex Behav. 2007;36(2):251-60.

478. Levine ME, Stern RM. Spatial task performance, sex differences, and motion sickness susceptibility. Percept Mot Skills. 2002;95(2):425-31.

479. Hugdahl K, Thomsen T, Ersland L. Sex differences in visuo-spatial processing: an fMRI study of mental rotation. Neuropsychologia. 2006;44(9):1575-83.

480. Jordan K, Wustenberg T, Heinze HJ, Peters M, Jancke L. Women and men exhibit different cortical activation patterns during mental rotation tasks. Neuropsychologia. 2002;40(13):2397-408.

481. Weiss E, Siedentopf CM, Hofer A, Deisenhammer EA, Hoptman MJ, Kremser C, et al. Sex differences in brain activation pattern during a visuospatial cognitive task: a functional magnetic resonance imaging study in healthy volunteers. Neurosci Lett. 2003;344(3):169-72.

482. Angelucci A, Bullier J. Reaching beyond the classical receptive field of V1 neurons: horizontal or feedback axons? J Physiol Paris. 2003;97(2-3):141-54.

483. Joseph J, Bae G, Silverstein SM. Sex, symptom, and premorbid social functioning associated with perceptual organization dysfunction in schizophrenia. Frontiers in psychology. 2013;4:547.

484. Perlick D, Mattis S, Stastny P, Teresi J. Gender differences in cognition in schizophrenia. Schizophr Res. 1992;8(1):69-73.

485. Krysta K, Murawiec S, Klasik A, Wiglusz MS, Krupka-Matuszczyk I. Sex-specific differences in cognitive functioning among schizophrenic patients. Psychiatria Danubina. 2013;25 Suppl 2:S244-6.

486. Mesholam-Gately RI, Giuliano AJ, Goff KP, Faraone SV, Seidman LJ. Neurocognition in first-episode schizophrenia: a meta-analytic review. Neuropsychology. 2009;23(3):315-36.

487. Mendrek A, Mancini-Marie A. Sex/gender differences in the brain and cognition in schizophrenia. Neurosci Biobehav Rev. 2016;67:57-78.

488. Melkersson KI, Hulting AL, Rane AJ. Dose requirement and prolactin elevation of antipsychotics in male and female patients with schizophrenia or related psychoses. British journal of clinical pharmacology. 2001;51(4):317-24.

489. Garyfallos G. [First-episode schizophrenia: Pharmacotherapy and psychosocial interventions]. Psychiatrike = Psychiatriki. 2007;18(1):29-46.

490. Tunnicliffe S, Harrison G, Standen PJ. Factors affecting compliance with depot injection treatment in the community. Social psychiatry and psychiatric epidemiology. 1992;27(5):230-3.

491. Robinson DG, Woerner MG, Alvir JM, Geisler S, Koreen A, Sheitman B, et al. Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. The American journal of psychiatry. 1999;156(4):544-9.

492. Usall J, Suarez D, Haro JM. Gender differences in response to antipsychotic treatment in outpatients with schizophrenia. Psychiatry research. 2007;153(3):225-31.

493. Pollock BG. Gender differences in psychotropic drug metabolism. Psychopharmacology bulletin. 1997;33(2):235-41.

494. Hogarty GE, Goldberg S, Schooler N. Proceedings: Drug and sociotherapy in the aftercare of schizophrenic patients. Psychopharmacology bulletin. 1974;10(4):47.

495. Hogarty GE, Goldberg SC, Schooler NR. Drug and sociotherapy in the aftercare of schizophrenic patients. III. Adjustment of nonrelapsed patients. Arch Gen Psychiatry. 1974;31(5):609-18.

496. Hogarty GE, Goldberg SC, Schooler NR, Ulrich RF. Drug and sociotherapy in the aftercare of schizophrenic patients. II. Two-year relapse rates. Arch Gen Psychiatry. 1974;31(5):603-8.

497. Seeman MV. Current outcome in schizophrenia: women vs men. Acta psychiatrica Scandinavica. 1986;73(6):609-17.

498. Seeman MV. Interaction of sex, age, and neuroleptic dose. Compr Psychiatry. 1983;24(2):125-8.

499. Lam RW, Peters R, Sladen-Dew N, Altman S. A community-based clinic survey of antidepressant use in persons with schizophrenia. Canadian journal of psychiatry Revue canadienne de psychiatrie. 1998;43(5):513-6.

500. Nyhuis AW, Faries DE, Ascher-Svanum H, Stauffer VL, Kinon BJ. Predictors of switching antipsychotic medications in the treatment of schizophrenia. BMC Psychiatry. 2010;10:75.

501. Rubin LH, Haas GL, Keshavan MS, Sweeney JA, Maki PM. Sex difference in cognitive response to antipsychotic treatment in first episode schizophrenia. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2008;33(2):290-7.

502. Akhondzadeh S, Nejatisafa AA, Amini H, Mohammadi MR, Larijani B, Kashani L, et al. Adjunctive estrogen treatment in women with chronic schizophrenia: a double-blind, randomized, and placebo-controlled trial. Prog Neuropsychopharmacol Biol Psychiatry. 2003;27(6):1007-12.

503. Louza MR, Marques AP, Elkis H, Bassitt D, Diegoli M, Gattaz WF. Conjugated estrogens as adjuvant therapy in the treatment of acute schizophrenia: a double-blind study. Schizophr Res. 2004;66(2-3):97-100.

504. Huerta-Ramos E, Iniesta R, Ochoa S, Cobo J, Miquel E, Roca M, et al. Effects of raloxifene on cognition in postmenopausal women with schizophrenia: a double-blind, randomized, placebo-controlled trial. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2014;24(2):223-31.

505. Huber TJ, Borsutzky M, Schneider U, Emrich HM. Psychotic disorders and gonadal function: evidence supporting the oestrogen hypothesis. Acta psychiatrica Scandinavica. 2004;109(4):269-74.

506. Brabban A, Tai S, Turkington D. Predictors of outcome in brief cognitive behavior therapy for schizophrenia. Schizophr Bull. 2009;35(5):859-64.

507. Gur RC, Gunning-Dixon F, Bilker WB, Gur RE. Sex differences in temporo-limbic and frontal brain volumes of healthy adults. Cereb Cortex. 2002;12(9):998-1003.

508. Gur RE, Gur RC. Gender differences in aging: cognition, emotions, and neuroimaging studies. Dialogues Clin Neurosci. 2002;4(2):197-210.

509. Harasty J, Double KL, Halliday GM, Kril JJ, McRitchie DA. Language-associated cortical regions are proportionally larger in the female brain. Arch Neurol. 1997;54(2):171-6.

510. Murphy DG, DeCarli C, McIntosh AR, Daly E, Mentis MJ, Pietrini P, et al. Sex differences in human brain morphometry and metabolism: an in vivo quantitative magnetic resonance imaging and positron emission tomography study on the effect of aging. Arch Gen Psychiatry. 1996;53(7):585-94.

511. Gur RE, Kohler C, Turetsky BI, Siegel SJ, Kanes SJ, Bilker WB, et al. A sexually dimorphic ratio of orbitofrontal to amygdala volume is altered in schizophrenia. Biol Psychiatry. 2004;55(5):512-7.

512. Savadjiev P, Whitford TJ, Hough ME, Clemm von Hohenberg C, Bouix S, Westin CF, et al. Sexually dimorphic white matter geometry abnormalities in adolescent onset schizophrenia. Cerebral cortex. 2014;24(5):1389-96.

513. Gur RE, Turetsky BI, Bilker WB, Gur RC. Reduced gray matter volume in schizophrenia. Arch Gen Psychiatry. 1999;56(10):905-11.

514. Paus T, Otaky N, Caramanos Z, MacDonald D, Zijdenbos A, D'Avirro D, et al. In vivo morphometry of the intrasulcal gray matter in the human cingulate, paracingulate, and superior-rostral sulci: hemispheric asymmetries, gender differences and probability maps. The Journal of comparative neurology. 1996;376(4):664-73.

515. Paus T, Tomaiuolo F, Otaky N, MacDonald D, Petrides M, Atlas J, et al. Human cingulate and paracingulate sulci: pattern, variability, asymmetry, and probabilistic map. Cerebral cortex. 1996;6(2):207-14.

516. Goldstein JM, Seidman LJ, Horton NJ, Makris N, Kennedy DN, Caviness VS, Jr., et al. Normal sexual dimorphism of the adult human brain assessed by in vivo magnetic resonance imaging. Cerebral cortex. 2001;11(6):490-7.

517. Andreasen NC, Flashman L, Flaum M, Arndt S, Swayze V, 2nd, O'Leary DS, et al. Regional brain abnormalities in schizophrenia measured with magnetic resonance imaging. JAMA. 1994;272(22):1763-9.

518. Andreasen NC, Ehrhardt JC, Swayze VW, 2nd, Alliger RJ, Yuh WT, Cohen G, et al. Magnetic resonance imaging of the brain in schizophrenia. The pathophysiologic significance of structural abnormalities. Arch Gen Psychiatry. 1990;47(1):35-44.

519. Reite M, Sheeder J, Teale P, Adams M, Richardson D, Simon J, et al. Magnetic source imaging evidence of sex differences in cerebral lateralization in schizophrenia. Arch Gen Psychiatry. 1997;54(5):433-40.

520. Gur RE, Cowell PE, Latshaw A, Turetsky BI, Grossman RI, Arnold SE, et al. Reduced dorsal and orbital prefrontal gray matter volumes in schizophrenia. Arch Gen Psychiatry. 2000;57(8):761-8.

521. Gur RE, Turetsky BI, Cowell PE, Finkelman C, Maany V, Grossman RI, et al. Temporolimbic volume reductions in schizophrenia. Arch Gen Psychiatry. 2000;57(8):769-75.

522. Castle DJ, Murray RM. The neurodevelopmental basis of sex differences in schizophrenia. Psychol Med. 1991;21(3):565-75.

523. Lewine RR, Hudgins P, Brown F, Caudle J, Risch SC. Differences in qualitative brain morphology findings in schizophrenia, major depression, bipolar disorder, and normal volunteers. Schizophr Res. 1995;15(3):253-9.

524. Bogerts B, Ashtari M, Degreef G, Alvir JM, Bilder RM, Lieberman JA. Reduced temporal limbic structure volumes on magnetic resonance images in first episode schizophrenia. Psychiatry research. 1990;35(1):1-13.

525. Flaum M, O'Leary DS, Swayze VW, 2nd, Miller DD, Arndt S, Andreasen NC. Symptom dimensions and brain morphology in schizophrenia and related psychotic disorders. J Psychiatr Res. 1995;29(4):261-76.

526. Flaum M, Swayze VW, 2nd, O'Leary DS, Yuh WT, Ehrhardt JC, Arndt SV, et al. Effects of diagnosis, laterality, and gender on brain morphology in schizophrenia. The American journal of psychiatry. 1995;152(5):704-14.

527. Lauriello J, Hoff A, Wieneke MH, Blankfeld H, Faustman WO, Rosenbloom M, et al. Similar extent of brain dysmorphology in severely ill women and men with schizophrenia. The American journal of psychiatry. 1997;154(6):819-25.

528. Vazquez-Barquero JL, Cuesta Nunez MJ, Quintana Pando F, de la Varga M, Herrera Castanedo S, Dunn G. Structural abnormalities of the brain in schizophrenia: sex differences in the Cantabria First Episode of Schizophrenia Study. Psychol Med. 1995;25(6):1247-57.

529. Johnstone EC, Crow TJ, Frith CD, Husband J, Kreel L. Cerebral ventricular size and cognitive impairment in chronic schizophrenia. Lancet. 1976;2(7992):924-6.

530. Cannon TD, Glahn DC, Kim J, Van Erp TG, Karlsgodt K, Cohen MS, et al. Dorsolateral prefrontal cortex activity during maintenance and manipulation of information in working memory in patients with schizophrenia. Arch Gen Psychiatry. 2005;62(10):1071-80.

531. Nopoulos P, Flaum M, Andreasen NC. Sex differences in brain morphology in schizophrenia. The American journal of psychiatry. 1997;154(12):1648-54.

532. Molina V, Sanz J, Sarramea F, Misiego JM, Benito C, Palomo T. Association between excessive frontal cerebrospinal fluid and illness duration in males but not in females with schizophrenia. Eur Psychiatry. 2005;20(4):332-8.

533. Narr KL, Sharma T, Woods RP, Thompson PM, Sowell ER, Rex D, et al. Increases in regional subarachnoid CSF without apparent cortical gray matter deficits in schizophrenia: modulating effects of sex and age. The American journal of psychiatry. 2003;160(12):2169-80.

534. Haijma SV, Van Haren N, Cahn W, Koolschijn PC, Hulshoff Pol HE, Kahn RS. Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. Schizophr Bull. 2013;39(5):1129-38.

535. Yotsutsuji T, Saitoh O, Suzuki M, Hagino H, Mori K, Takahashi T, et al. Quantification of lateral ventricular subdivisions in schizophrenia by high-resolution three-dimensional magnetic resonance imaging. Psychiatry research. 2003;122(1):1-12.

536. Collinson SL, Mackay CE, James AC, Quested DJ, Phillips T, Roberts N, et al. Brain volume, asymmetry and intellectual impairment in relation to sex in early-onset schizophrenia. The British journal of psychiatry : the journal of mental science. 2003;183:114-20.

537. Bryant NL, Buchanan RW, Vladar K, Breier A, Rothman M. Gender differences in temporal lobe structures of patients with schizophrenia: a volumetric MRI study. The American journal of psychiatry. 1999;156(4):603-9.

538. Heckers S, Goff D, Schacter DL, Savage CR, Fischman AJ, Alpert NM, et al. Functional imaging of memory retrieval in deficit vs nondeficit schizophrenia. Arch Gen Psychiatry. 1999;56(12):1117-23.

539. Smith GN, Thornton AE, Lang DJ, Macewan GW, Ehmann TS, Kopala LC, et al. Hippocampal volume and the brain-derived neurotrophic factor Val66Met polymorphism in first episode psychosis. Schizophr Res. 2012;134(2-3):253-9.

540. Irle E, Lange C, Ruhleder M, Exner C, Siemerkus J, Weniger G. Hippocampal size in women but not men with schizophrenia relates to disorder duration. Psychiatry research. 2011;192(3):133-9.

541. Verma S, Sitoh YY, Ho YC, Poon LY, Subramaniam M, Chan YH, et al. Hippocampal volumes in first-episode psychosis. J Neuropsychiatry Clin Neurosci. 2009;21(1):24-9.

542. Gur RE, Cowell P, Turetsky BI, Gallacher F, Cannon T, Bilker W, et al. A follow-up magnetic resonance imaging study of schizophrenia. Relationship of neuroanatomical changes to clinical and neurobehavioral measures. Arch Gen Psychiatry. 1998;55(2):145-52.

543. Arciniegas D, Rojas DC, Teale P, Sheeder J, Sandberg E, Reite M. The thalamus and the schizophrenia phenotype: failure to replicate reduced volume. Biol Psychiatry. 1999;45(10):1329-35.

544. Niu L, Matsui M, Zhou SY, Hagino H, Takahashi T, Yoneyama E, et al. Volume reduction of the amygdala in patients with schizophrenia: a magnetic resonance imaging study. Psychiatry research. 2004;132(1):41-51.

545. Goghari VM, Smith GN, Honer WG, Kopala LC, Thornton AE, Su W, et al. Effects of eight weeks of atypical antipsychotic treatment on middle frontal thickness in drug-naive first-episode psychosis patients. Schizophr Res. 2013;149(1-3):149-55.

546. Gilmore JH, Lin W, Prastawa MW, Looney CB, Vetsa YS, Knickmeyer RC, et al. Regional gray matter growth, sexual dimorphism, and cerebral asymmetry in the neonatal brain. J Neurosci. 2007;27(6):1255-60.

547. Frederikse M, Lu A, Aylward E, Barta P, Sharma T, Pearlson G. Sex differences in inferior parietal lobule volume in schizophrenia. The American journal of psychiatry. 2000;157(3):422-7.

548. Takayanagi Y, Takahashi T, Orikabe L, Mozue Y, Kawasaki Y, Nakamura K, et al. Classification of first-episode schizophrenia patients and healthy subjects by automated MRI measures of regional brain volume and cortical thickness. PLoS One. 2011;6(6):e21047.

549. Nesvag R, Lawyer G, Varnas K, Fjell AM, Walhovd KB, Frigessi A, et al. Regional thinning of the cerebral cortex in schizophrenia: effects of diagnosis, age and antipsychotic medication. Schizophr Res. 2008;98(1-3):16-28.

550. Duggal HS, Muddasani S, Keshavan MS. Insular volumes in first-episode schizophrenia: gender effect. Schizophr Res. 2005;73(1):113-20.

551. Goldstein JM, Seidman LJ, O'Brien LM, Horton NJ, Kennedy DN, Makris N, et al. Impact of normal sexual dimorphisms on sex differences in structural brain abnormalities in schizophrenia assessed by magnetic resonance imaging. Arch Gen Psychiatry. 2002;59(2):154-64.

552. Takahashi T, Suzuki M, Kawasaki Y, Hagino H, Yamashita I, Nohara S, et al. Perigenual cingulate gyrus volume in patients with schizophrenia: a magnetic resonance imaging study. Biol Psychiatry. 2003;53(7):593-600.

553. Abbs B, Liang L, Makris N, Tsuang M, Seidman LJ, Goldstein JM. Covariance modeling of MRI brain volumes in memory circuitry in schizophrenia: Sex differences are critical. Neuroimage. 2011;56(4):1865-74.

554. Narr KL, Toga AW, Szeszko P, Thompson PM, Woods RP, Robinson D, et al. Cortical thinning in cingulate and occipital cortices in first episode schizophrenia. Biol Psychiatry. 2005;58(1):32-40.

555. Narr KL, Bilder RM, Kim S, Thompson PM, Szeszko P, Robinson D, et al. Abnormal gyral complexity in first-episode schizophrenia. Biol Psychiatry. 2004;55(8):859-67.

556. Highley JR, DeLisi LE, Roberts N, Webb JA, Relja M, Razi K, et al. Sex-dependent effects of schizophrenia: an MRI study of gyral folding, and cortical and white matter volume. Psychiatry Res. 2003;124(1):11-23.

557. Sallet PC, Elkis H, Alves TM, Oliveira JR, Sassi E, Campi de Castro C, et al. Reduced cortical folding in schizophrenia: an MRI morphometric study. Am J Psychiatry. 2003;160(9):1606-13.

558. Vogeley K, Schneider-Axmann T, Pfeiffer U, Tepest R, Bayer TA, Bogerts B, et al. Disturbed gyrification of the prefrontal region in male schizophrenic patients: A morphometric postmortem study. Am J Psychiatry. 2000;157(1):34-9.

559. Narr K, Thompson P, Sharma T, Moussai J, Zoumalan C, Rayman J, et al. Three-dimensional mapping of gyral shape and cortical surface asymmetries in schizophrenia: gender effects. Am J Psychiatry. 2001;158(2):244-55.

560. Bullmore E, Brammer M, Harvey I, Murray R, Ron M. Cerebral hemispheric asymmetry revisited: effects of handedness, gender and schizophrenia measured by radius of gyration in magnetic resonance images. Psychol Med. 1995;25(2):349-63.

561. Flaum M, Arndt S, Andreasen NC. The role of gender in studies of ventricle enlargement in schizophrenia: a predominantly male effect. Am J Psychiatry. 1990;147(10):1327-32.

562. Narr KL, Bilder RM, Toga AW, Woods RP, Rex DE, Szeszko PR, et al. Mapping cortical thickness and gray matter concentration in first episode schizophrenia. Cereb Cortex. 2005;15(6):708-19.

563. Narr KL, Toga AW, Szeszko P, Thompson PM, Woods RP, Robinson D, et al. Cortical thinning in cingulate and occipital cortices in first episode schizophrenia. Biol Psychiatry. 2005;58(1):32-40.

564. Lewine RR, Hudgins P, Brown F, Caudle J, Risch SC. Differences in qualitative brain morphology findings in schizophrenia, major depression, bipolar disorder, and normal volunteers. Schizophr Res. 1995;15(3):253-9.

565. Highley JR, DeLisi LE, Roberts N, Webb JA, Relja M, Razi K, et al. Sex-dependent effects of schizophrenia: an MRI study of gyral folding, and cortical and white matter volume. Psychiatry research. 2003;124(1):11-23.

566. Narr KL, Bilder RM, Woods RP, Thompson PM, Szeszko P, Robinson D, et al. Regional specificity of cerebrospinal fluid abnormalities in first episode schizophrenia. Psychiatry research. 2006;146(1):21-33.

567. Narr KL, Thompson PM, Sharma T, Moussai J, Cannestra AF, Toga AW. Mapping morphology of the corpus callosum in schizophrenia. Cerebral cortex. 2000;10(1):40-9.

568. Narr KL, Woods RP, Lin J, Kim J, Phillips OR, Del'Homme M, et al. Widespread cortical thinning is a robust anatomical marker for attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2009;48(10):1014-22.

569. Okugawa G, Sedvall GC, Agartz I. Smaller cerebellar vermis but not hemisphere volumes in patients with chronic schizophrenia. The American journal of psychiatry. 2003;160(9):1614-7.

570. Crow TJ. The 'big bang' theory of the origin of psychosis and the faculty of language. Schizophr Res. 2008;102(1-3):31-52.

571. Crow TJ. The 'big bang' theory of the origin of psychosis and the faculty of language. Schizophr Res. 2008;102(1-3):31-52.

572. DeLisi LE, Hoff AL, Neale C, Kushner M. Asymmetries in the superior temporal lobe in male and female first-episode schizophrenic patients: measures of the planum temporale and superior temporal gyrus by MRI. Schizophr Res. 1994;12(1):19-28.

573. Pruessner M, Boekestyn L, Bechard-Evans L, Abadi S, Vracotas N, Joober R, et al. Sex differences in the cortisol response to awakening in recent onset psychosis. Psychoneuroendocrinology. 2008;33(8):1151-4.

574. Jansen LM, Gispen-de Wied CC, Gademan PJ, De Jonge RC, van der Linden JA, Kahn RS. Blunted cortisol response to a psychosocial stressor in schizophrenia. Schizophr Res. 1998;33(1-2):87-94.

575. Schmitt A, Schulenberg W, Bernstein HG, Steiner J, Schneider-Axmann T, Yeganeh-Doost P, et al. Reduction of gyrification index in the cerebellar vermis in schizophrenia: a post-mortem study. The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry. 2011;12 Suppl 1:99-103.

576. Hugdahl K, Loberg EM, Nygard M. Left temporal lobe structural and functional abnormality underlying auditory hallucinations in schizophrenia. Front Neurosci. 2009;3(1):34-45.

577. Williams LM. Voxel-based morphometry in schizophrenia: implications for neurodevelopmental connectivity models, cognition and affect. Expert Rev Neurother. 2008;8(7):1049-65.

578. Salgado-Pineda P, Caclin A, Baeza I, Junque C, Bernardo M, Blin O, et al. Schizophrenia and frontal cortex: where does it fail? Schizophr Res. 2007;91(1-3):73-81.

579. Dazzan P, Soulsby B, Mechelli A, Wood SJ, Velakoulis D, Phillips LJ, et al. Volumetric abnormalities predating the onset of schizophrenia and affective psychoses: an MRI study in subjects at ultrahigh risk of psychosis. Schizophr Bull. 2012;38(5):1083-91.

580. Kong L, Herold CJ, Zollner F, Salat DH, Lasser MM, Schmid LA, et al. Comparison of grey matter volume and thickness for analysing cortical changes in chronic schizophrenia: A matter of surface area, grey/white matter intensity contrast, and curvature. Psychiatry research. 2014.

581. Crossley NA, Mechelli A, Scott J, Carletti F, Fox PT, McGuire P, et al. The hubs of the human connectome are generally implicated in the anatomy of brain disorders. Brain. 2014;137(Pt 8):2382-95.

582. Hietala J, Syvalahti E, Vuorio K, Rakkolainen V, Bergman J, Haaparanta M, et al. Presynaptic dopamine function in striatum of neuroleptic-naive schizophrenic patients. Lancet. 1995;346(8983):1130-1.

583. Hutcheson NL, Clark DG, Bolding MS, White DM, Lahti AC. Basal ganglia volume in unmedicated patients with schizophrenia is associated with treatment response to antipsychotic medication. Psychiatry research. 2014;221(1):6-12.

584. Craig AD. Emotional moments across time: a possible neural basis for time perception in the anterior insula. Philos Trans R Soc Lond B Biol Sci. 2009;364(1525):1933-42.

585. Rolland B, Amad A, Poulet E, Bordet R, Vignaud A, Bation R, et al. Resting-state functional connectivity of the nucleus accumbens in auditory and visual hallucinations in schizophrenia. Schizophr Bull. 2015;41(1):291-9.

586. Supekar K, Menon V. Developmental maturation of dynamic causal control signals in higher-order cognition: a neurocognitive network model. PLoS computational biology. 2012;8(2):e1002374.

587. Cauda F, Cavanna AE, D'Agata F, Sacco K, Duca S, Geminiani GC. Functional connectivity and coactivation of the nucleus accumbens: a combined functional connectivity and structure-based meta-analysis. J Cogn Neurosci. 2011;23(10):2864-77.

588. Kurth F, Zilles K, Fox PT, Laird AR, Eickhoff SB. A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. Brain structure & function. 2010;214(5-6):519-34.

589. Mutschler I, Wieckhorst B, Kowalevski S, Derix J, Wentlandt J, Schulze-Bonhage A, et al. Functional organization of the human anterior insular cortex. Neuroscience letters. 2009;457(2):66-70.

590. Nesvag R, Saetre P, Lawyer G, Jonsson EG, Agartz I. The relationship between symptom severity and regional cortical and grey matter volumes in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33(3):482-90.

591. Golkar A, Lonsdorf TB, Olsson A, Lindstrom KM, Berrebi J, Fransson P, et al. Distinct contributions of the dorsolateral prefrontal and orbitofrontal cortex during emotion regulation. PLoS One. 2012;7(11):e48107.

592. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: The neural basis of normal emotion perception. Biol Psychiatry. 2003;54(5):504-14.

593. Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD. Rethinking feelings: an FMRI study of the cognitive regulation of emotion. J Cogn Neurosci. 2002;14(8):1215-29.

594. Pena-Gomez C, Vidal-Pineiro D, Clemente IC, Pascual-Leone A, Bartres-Faz D. Down-regulation of negative emotional processing by transcranial direct current stimulation: effects of personality characteristics. PLoS One. 2011;6(7):e22812.

595. O'Driscoll C, Laing J, Mason O. Cognitive emotion regulation strategies, alexithymia and dissociation in schizophrenia, a review and meta-analysis. Clin Psychol Rev. 2014;34(6):482-95.

596. Roberts AC, Wallis JD. Inhibitory control and affective processing in the prefrontal cortex: neuropsychological studies in the common marmoset. Cereb Cortex. 2000;10(3):252-62.

597. Bonelli RM, Cummings JL. Frontal-subcortical circuitry and behavior. Dialogues Clin Neurosci. 2007;9(2):141-51.

598. Miller BL, Darby A, Benson DF, Cummings JL, Miller MH. Aggressive, socially disruptive and antisocial behaviour associated with fronto-temporal dementia. The British journal of psychiatry : the journal of mental science. 1997;170:150-4.

599. Smith R, Chen K, Baxter L, Fort C, Lane RD. Antidepressant effects of sertraline associated with volume increases in dorsolateral prefrontal cortex. J Affect Disord. 2013;146(3):414-9.

600. Asami T, Hyuk Lee S, Bouix S, Rathi Y, Whitford TJ, Niznikiewicz M, et al. Cerebral white matter abnormalities and their associations with negative but not positive symptoms of schizophrenia. Psychiatry research. 2014;222(1-2):52-9.

601. Langdon R, Ward PB, Coltheart M. Reasoning anomalies associated with delusions in schizophrenia. Schizophr Bull. 2010;36(2):321-30.

602. Wendelken C. Meta-analysis: how does posterior parietal cortex contribute to reasoning? Frontiers in human neuroscience. 2014;8:1042.

603. Andreasen NC, Shore D, Burke JD, Jr., Grove WM, Lieberman JA, Oltmanns TF, et al. Clinical phenomenology. Schizophr Bull. 1988;14(3):345-63.

604. Andreasen NC, Pierson R. The role of the cerebellum in schizophrenia. Biol Psychiatry. 2008;64(2):81-8.

605. Stoodley CJ, Schmahmann JD. Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. Cortex. 2010;46(7):831-44.

606. Laroi F, Woodward TS. Hallucinations from a cognitive perspective. Harv Rev Psychiatry. 2007;15(3):109-17.

607. Allen PP, Johns LC, Fu CH, Broome MR, Vythelingum GN, McGuire PK. Misattribution of external speech in patients with hallucinations and delusions. Schizophr Res. 2004;69(2-3):277-87.

608. Seal ML, Aleman A, McGuire PK. Compelling imagery, unanticipated speech and deceptive memory: neurocognitive models of auditory verbal hallucinations in schizophrenia. Cogn Neuropsychiatry. 2004;9(1-2):43-72.

609. Tracy DK, Shergill SS. Mechanisms Underlying Auditory Hallucinations-Understanding Perception without Stimulus. Brain Sci. 2013;3(2):642-69.

610. Sugimori E, Mitchell KJ, Raye CL, Greene EJ, Johnson MK. Brain mechanisms underlying reality monitoring for heard and imagined words. Psychol Sci. 2014;25(2):403-13.

611. Thoresen C, Endestad T, Sigvartsen NP, Server A, Bolstad I, Johansson M, et al. Frontotemporal hypoactivity during a reality monitoring paradigm is associated with delusions in patients with schizophrenia spectrum disorders. Cogn Neuropsychiatry. 2014;19(2):97-115.

612. Hoptman MJ, D'Angelo D, Catalano D, Mauro CJ, Shehzad ZE, Kelly AM, et al. Amygdalofrontal functional disconnectivity and aggression in schizophrenia. Schizophr Bull. 2010;36(5):1020-8.

613. Hoptman MJ, Volavka J, Johnson G, Weiss E, Bilder RM, Lim KO. Frontal white matter microstructure, aggression, and impulsivity in men with schizophrenia: a preliminary study. Biol Psychiatry. 2002;52(1):9-14.

614. Herbert MR, Ziegler DA, Makris N, Filipek PA, Kemper TL, Normandin JJ, et al. Localization of white matter volume increase in autism and developmental language disorder. Ann Neurol. 2004;55(4):530-40.

615. Gaser C, Nenadic I, Volz HP, Buchel C, Sauer H. Neuroanatomy of "hearing voices": a frontotemporal brain structural abnormality associated with auditory hallucinations in schizophrenia. Cerebral cortex. 2004;14(1):91-6.

616. Garcia-Marti G, Aguilar EJ, Lull JJ, Marti-Bonmati L, Escarti MJ, Manjon JV, et al. Schizophrenia with auditory hallucinations: a voxel-based morphometry study. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(1):72-80.

617. Aguilar EJ, Sanjuan J, Garcia-Marti G, Lull JJ, Robles M. MR and genetics in schizophrenia: focus on auditory hallucinations. Eur J Radiol. 2008;67(3):434-9.

618. Hu HH, Guo WY, Chen HY, Wang PS, Hung CI, Hsieh JC, et al. Morphological regionalization using fetal magnetic resonance images of normal developing brains. Eur J Neurosci. 2009;29(8):1560-7.

619. Arango C, Kahn R. Progressive brain changes in schizophrenia. Schizophr Bull. 2008;34(2):310-1.

620. Cahn W, Hulshoff Pol HE, Bongers M, Schnack HG, Mandl RC, Van Haren NE, et al. Brain morphology in antipsychotic-naive schizophrenia: a study of multiple brain structures. Br J Psychiatry Suppl. 2002;43:s66-72.

621. Cahn W, Hulshoff Pol HE, Lems EB, van Haren NE, Schnack HG, van der Linden JA, et al. Brain volume changes in first-episode schizophrenia: a 1-year follow-up study. Arch Gen Psychiatry. 2002;59(11):1002-10.

622. DeLisi LE, Sakuma M, Tew W, Kushner M, Hoff AL, Grimson R. Schizophrenia as a chronic active brain process: a study of progressive brain structural change subsequent to the onset of schizophrenia. Psychiatry Res. 1997;74(3):129-40.

623. DeLisi LE, Tew W, Xie S, Hoff AL, Sakuma M, Kushner M, et al. A prospective follow-up study of brain morphology and cognition in first-episode schizophrenic patients: preliminary findings. Biol Psychiatry. 1995;38(6):349-60.

624. Lieberman J, Chakos M, Wu H, Alvir J, Hoffman E, Robinson D, et al. Longitudinal study of brain morphology in first episode schizophrenia. Biol Psychiatry. 2001;49(6):487-99.

625. Wood SJ, Pantelis C, Velakoulis D, Yucel M, Fornito A, McGorry PD. Progressive changes in the development toward schizophrenia: studies in subjects at increased symptomatic risk. Schizophr Bull. 2008;34(2):322-9.

626. Brans RG, van Haren NE, van Baal GC, Staal WG, Schnack HG, Kahn RS, et al. Longitudinal MRI study in schizophrenia patients and their healthy siblings. Br J Psychiatry. 2008;193(5):422-3.

627. Cahn W, Rais M, Stigter FP, van Haren NE, Caspers E, Hulshoff Pol HE, et al. Psychosis and brain volume changes during the first five years of schizophrenia. Eur Neuropsychopharmacol. 2009;19(2):147-51.

628. Hulshoff Pol HE, Kahn RS. What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. Schizophr Bull. 2008;34(2):354-66.

629. Velakoulis D, Wood SJ, Smith DJ, Soulsby B, Brewer W, Leeton L, et al. Increased duration of illness is associated with reduced volume in right medial temporal/anterior cingulate grey matter in patients with chronic schizophrenia. Schizophr Res. 2002;57(1):43-9.

630. Mazhari S, Moghadas Tabrizi Y. Abnormalities of mental rotation of hands associated with speed of information processing and executive function in chronic schizophrenic patients. Psychiatry Clin Neurosci. 2014;68(6):410-7.

631. Wang Q, Cheung C, Deng W, Li M, Huang C, Ma X, et al. Fronto-parietal white matter microstructural deficits are linked to performance IQ in a first-episode schizophrenia Han Chinese sample. Psychol Med. 2013;43(10):2047-56.

632. Tagamets MA, Cortes CR, Griego JA, Elvevag B. Neural correlates of the relationship between discourse coherence and sensory monitoring in schizophrenia. Cortex. 2014;55:77-87.

633. Yun JY, Hur JW, Jung WH, Jang JH, Youn T, Kang DH, et al. Dysfunctional role of parietal lobe during self-face recognition in schizophrenia. Schizophr Res. 2014;152(1):81-8.

634. Lakis N. An fMRI study of emotional episodic memory in schizophrenia: Effects of diagnosis and sex. Montreal, Quebec, Canada: University of Montreal; 2012.

635. Lakis N, Jimenez JA, Mancini-Marie A, Stip E, Lavoie ME, Mendrek A. Neural correlates of emotional recognition memory in schizophrenia: effects of valence and arousal. Psychiatry research. 2011;194(3):245-56.

636. Ongur D, Cullen TJ, Wolf DH, Rohan M, Barreira P, Zalesak M, et al. The neural basis of relational memory deficits in schizophrenia. Arch Gen Psychiatry. 2006;63(4):356-65.

637. Kaller CP, Loosli SV, Rahm B, Gossel A, Schieting S, Hornig T, et al. Working memory in schizophrenia: behavioral and neural evidence for reduced susceptibility to item-specific proactive interference. Biol Psychiatry. 2014;76(6):486-94.

638. Eich TS, Nee DE, Insel C, Malapani C, Smith EE. Neural correlates of impaired cognitive control over working memory in schizophrenia. Biol Psychiatry. 2014;76(2):146-53.

639. Fioravanti M, Carlone O, Vitale B, Cinti ME, Clare L. A meta-analysis of cognitive deficits in adults with a diagnosis of schizophrenia. Neuropsychology review. 2005;15(2):73-95.

640. Gold JM, Harvey PD. Cognitive deficits in schizophrenia. The Psychiatric clinics of North America. 1993;16(2):295-312.

641. Gold JM, Weinberger DR. Cognitive deficits and the neurobiology of schizophrenia. Curr Opin Neurobiol. 1995;5(2):225-30.

642. Wolf C, Linden S, Jackson MC, Healy D, Baird A, Linden DE, et al. Brain activity supporting working memory accuracy in patients with paranoid schizophrenia: a functional magnetic resonance imaging study. Neuropsychobiology. 2011;64(2):93-101.

643. Cabeza R, Ciaramelli E, Olson IR, Moscovitch M. The parietal cortex and episodic memory: an attentional account. Nature reviews Neuroscience. 2008;9(8):613-25.

644. Niznikiewicz M, Donnino R, McCarley RW, Nestor PG, Iosifescu DV, O'Donnell B, et al. Abnormal angular gyrus asymmetry in schizophrenia. The American journal of psychiatry. 2000;157(3):428-37.

645. Lepage M, Pelletier M, Achim A, Montoya A, Menear M, Lal S. Parietal cortex and episodic memory retrieval in schizophrenia. Psychiatry research. 2010;182(3):191-9.

646. Barch DM, Csernansky JG. Abnormal parietal cortex activation during working memory in schizophrenia: verbal phonological coding disturbances versus domain-general executive dysfunction. The American journal of psychiatry. 2007;164(7):1090-8.

647. Binder JR, Desai RH, Graves WW, Conant LL. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cerebral cortex. 2009;19(12):2767-96.

648. Chambers CD, Payne JM, Stokes MG, Mattingley JB. Fast and slow parietal pathways mediate spatial attention. Nature neuroscience. 2004;7(3):217-8.

649. Pearlson GD, Petty RG, Ross CA, Tien AY. Schizophrenia: a disease of heteromodal association cortex? Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 1996;14(1):1-17.

650. Rametti G, Segarra N, Junque C, Bargallo N, Caldu X, Ibarretxe N, et al. Left posterior hippocampal density reduction using VBM and stereological MRI procedures in schizophrenia. Schizophr Res. 2007;96(1-3):62-71.

651. Honey CJ, Sporns O, Cammoun L, Gigandet X, Thiran JP, Meuli R, et al. Predicting human resting-state functional connectivity from structural connectivity. Proceedings of the National Academy of Sciences of the United States of America. 2009;106(6):2035-40.

652. Skelley SL, Goldberg TE, Egan MF, Weinberger DR, Gold JM. Verbal and visual memory: characterizing the clinical and intermediate phenotype in schizophrenia. Schizophr Res. 2008;105(1-3):78-85.

653. Plessen KJ, Hugdahl K, Bansal R, Hao X, Peterson BS. Sex, age, and cognitive correlates of asymmetries in thickness of the cortical mantle across the life span. J Neurosci. 2014;34(18):6294-302.

654. van Lutterveld R, van den Heuvel MP, Diederen KM, de Weijer AD, Begemann MJ, Brouwer RM, et al. Cortical thickness in individuals with non-clinical and clinical psychotic symptoms. Brain. 2014;137(Pt 10):2664-9.

655. Graux J, Bidet-Caulet A, Bonnet-Brilhault F, Camus V, Bruneau N. Hallucinations and negative symptoms differentially revealed by frontal and temporal responses to speech in schizophrenia. Schizophr Res. 2014;155(1-3):39-44.

656. Nenadic I, Yotter RA, Sauer H, Gaser C. Cortical surface complexity in frontal and temporal areas varies across subgroups of schizophrenia. Human brain mapping. 2014;35(4):1691-9.

657. Bodnar M, Hovington CL, Buchy L, Malla AK, Joober R, Lepage M. Cortical thinning in temporo-parietal junction (TPJ) in non-affective first-episode of psychosis patients with persistent negative symptoms. PLoS One. 2014;9(6):e101372.

658. Arango C, Kahn R. Progressive brain changes in schizophrenia. Schizophr Bull. 2008;34(2):310-1.

659. Brans RG, van Haren NE, van Baal GC, Staal WG, Schnack HG, Kahn RS, et al. Longitudinal MRI study in schizophrenia patients and their healthy siblings. The British journal of psychiatry : the journal of mental science. 2008;193(5):422-3.

660. Hulshoff Pol HE, Kahn RS. What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. Schizophr Bull. 2008;34(2):354-66.

661. Wood SJ, Pantelis C, Velakoulis D, Yucel M, Fornito A, McGorry PD. Progressive changes in the development toward schizophrenia: studies in subjects at increased symptomatic risk. Schizophr Bull. 2008;34(2):322-9.

662. Cahn W, Rais M, Stigter FP, van Haren NE, Caspers E, Hulshoff Pol HE, et al. Psychosis and brain volume changes during the first five years of schizophrenia. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2009;19(2):147-51.

663. Geschwind N, Galaburda AM. Cerebral lateralization. Biological mechanisms, associations, and pathology: I. A hypothesis and a program for research. Arch Neurol. 1985;42(5):428-59.

664. Seeman MV. Prenatal gonadal hormones and schizophrenia in men and women. Psychiatric journal of the University of Ottawa : Revue de psychiatrie de l'Universite d'Ottawa. 1989;14(3):473-5.

665. Crow TJ, Chance SA, Priddle TH, Radua J, James AC. Laterality interacts with sex across the schizophrenia/bipolarity continuum: an interpretation of meta-analyses of structural MRI. Psychiatry research. 2013;210(3):1232-44.

666. Jou RJ, Hardan AY, Keshavan MS. Reduced cortical folding in individuals at high risk for schizophrenia: a pilot study. Schizophr Res. 2005;75(2-3):309-13.

667. Onitsuka T, McCarley RW, Kuroki N, Dickey CC, Kubicki M, Demeo SS, et al. Occipital lobe gray matter volume in male patients with chronic schizophrenia: A quantitative MRI study. Schizophr Res. 2007;92(1-3):197-206.

668. Bijanki KR, Hodis B, Magnotta VA, Zeien E, Andreasen NC. Effects of age on white matter integrity and negative symptoms in schizophrenia. Schizophr Res. 2015;161(1):29-35.

669. Mitelman SA, Shihabuddin L, Brickman AM, Hazlett EA, Buchsbaum MS. MRI assessment of gray and white matter distribution in Brodmann's areas of the cortex in patients with

schizophrenia with good and poor outcomes. The American journal of psychiatry. 2003;160(12):2154-68.

670. Batty MJ, Liddle EB, Pitiot A, Toro R, Groom MJ, Scerif G, et al. Cortical gray matter in attention-deficit/hyperactivity disorder: a structural magnetic resonance imaging study. Journal of the American Academy of Child and Adolescent Psychiatry. 2010;49(3):229-38.

671. Ronald A, Sieradzka D, Cardno AG, Haworth CM, McGuire P, Freeman D. Characterization of psychotic experiences in adolescence using the specific psychotic experiences questionnaire: findings from a study of 5000 16-year-old twins. Schizophr Bull. 2014;40(4):868-77.

672. Wigman JT, Vollebergh WA, Raaijmakers QA, Iedema J, van Dorsselaer S, Ormel J, et al. The structure of the extended psychosis phenotype in early adolescence--a cross-sample replication. Schizophr Bull. 2011;37(4):850-60.

673. Sallet PC, Elkis H, Alves TM, Oliveira JR, Sassi E, Campi de Castro C, et al. Reduced cortical folding in schizophrenia: an MRI morphometric study. The American journal of psychiatry. 2003;160(9):1606-13.

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

675. Lei W, Li M, Deng W, Zhou Y, Ma X, Wang Q, et al. Sex-Specific Patterns of Aberrant Brain Function in First-Episode Treatment-Naive Patients with Schizophrenia. International journal of molecular sciences. 2015;16(7):16125-43.

676. Lang PJ, Bradley MM, Cuthbert BN. International Affective Picture System (IAPS): Technical Manual and Affective. . Gainesville, FL: NIMH Center for the Study of Emotion and Attention, University of Florida.; 1997.

677. Ross CA, Pearlson GD. Schizophrenia, the heteromodal association neocortex and development: potential for a neurogenetic approach. Trends in neurosciences. 1996;19(5):171-6.

678. Ellison-Wright I, Bullmore E. Meta-analysis of diffusion tensor imaging studies in schizophrenia. Schizophr Res. 2009;108(1-3):3-10.

679. Ellison-Wright I, Bullmore E. Anatomy of bipolar disorder and schizophrenia: a meta-analysis. Schizophr Res. 2010;117(1):1-12.

680. Alexander-Bloch AF, Vertes PE, Stidd R, Lalonde F, Clasen L, Rapoport J, et al. The anatomical distance of functional connections predicts brain network topology in health and schizophrenia. Cerebral cortex. 2013;23(1):127-38.

681. Cohen AS, Minor KS. Emotional experience in patients with schizophrenia revisited: meta-analysis of laboratory studies. Schizophr Bull. 2010;36(1):143-50.

682. Kring AM, Gordon AH. Sex differences in emotion: expression, experience, and physiology. Journal of personality and social psychology. 1998;74(3):686-703.

683. Myin-Germeys I, van Os J, Schwartz JE, Stone AA, Delespaul PA. Emotional reactivity to daily life stress in psychosis. Arch Gen Psychiatry. 2001;58(12):1137-44.

684. Phillips LJ, Francey SM, Edwards J, McMurray N. Strategies used by psychotic individuals to cope with life stress and symptoms of illness: a systematic review. Anxiety, stress, and coping. 2009;22(4):371-410.

685. Matud MP. Gender differences in stress and coping styles. Personality and Individual Differences. 2004;37:1401-15.

686. Kendler KS, Thornton LM, Prescott CA. Gender differences in the rates of exposure to stressful life events and sensitivity to their depressogenic effects. Am J Psychiatry. 2001;158(4):587-93.

687. Brougham RR, Zail, C. M., Mendoza, C. M., Miller, J. R. . Stress, sex differences, and coping strategies among college students. Current Psychology 2009;28:85-97.

688. Wang L, Li Y, Metzak P, He Y, Woodward TS. Age-related changes in topological patterns of large-scale brain functional networks during memory encoding and recognition. Neuroimage. 2010;50(3):862-72.

689. Riecher-Rossler A, Hafner H, Dutsch-Strobel A, Oster M, Stumbaum M, van Gulick-Bailer M, et al. Further evidence for a specific role of estradiol in schizophrenia? Biol Psychiatry. 1994;36(7):492-4.

690. Riecher-Rossler A, Hafner H, Stumbaum M, Maurer K, Schmidt R. Can estradiol modulate schizophrenic symptomatology? Schizophr Bull. 1994;20(1):203-14.

691. Holdcroft A. Gender bias in research: how does it affect evidence based medicine? J R Soc Med. 2007;100(1):2-3.

692. Holdcroft A. Integrating the dimensions of sex and gender into basic life sciences research: methodologic and ethical issues. Gender medicine. 2007;4 Suppl B:S64-74.

693. Mazure CM, Jones DP. Twenty years and still counting: including women as participants and studying sex and gender in biomedical research. BMC women's health. 2015;15:94.

694. Mendrek A. Is It Important to Consider Sex and Gender in Neurocognitive Studies? Front Psychiatry. 2015;6:83.

695. Winkler AM, Kochunov P, Blangero J, Almasy L, Zilles K, Fox PT, et al. Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. Neuroimage. 2010;53(3):1135-46.

696. Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. The Journal of clinical psychiatry. 2003;64(6):663-7.

697. Mortimer AM. Symptom rating scales and outcome in schizophrenia. Br J Psychiatry Suppl. 2007;50:s7-14.

698. Stip E, Fahim C, Liddle P, Mancini-Marie A, Mensour B, Bentaleb LA, et al. Neural correlates of sad feelings in schizophrenia with and without blunted affect. Can J Psychiatry. 2005;50(14):909-17.

699. Stip E, Fahim C, Mancini-Marie A, Bentaleb LA, Mensour B, Mendrek A, et al. Restoration of frontal activation during a treatment with quetiapine: an fMRI study of blunted affect in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2005;29(1):21-6.

700. First MB. Harmonisation of ICD-11 and DSM-V: opportunities and challenges. The British journal of psychiatry : the journal of mental science. 2009;195(5):382-90.

701. First MB. Reorganizing the diagnostic groupings in DSM-V and ICD-11: a cost/benefit analysis. Psychol Med. 2009;39(12):2091-7.

12 **Appendix**

- Fourth article: Adrianna Mendrek and Adham Mancini-Marïe. Sex/gender differences in the brain and cognition in schizophrenia. Neuroscience and Biobehavioral Reviews 2016 Aug; 67:57-78.

Table X. The summary of studies investigating sex differences in brain structure of schizophrenia patients

Study ref	Diagnosis (N)	Patients M:F	Age (Mean)	Healthy N= M:F	Age (Mean)	region	approach	findings
Lang et al 2006	29 FEP 26 SZ 2 SZA 1 psychosis not otherwise specified	21:8	22.0 (5.1)	N=22 12:10	24.7 (6.4)	Thalamus	MRI A single rater manual volumetric measures	Male FEP but not females subjects showed significantly smaller right Anterior internal capsule volumes compared to healthy volunteers
Andreasen et al 1994.	SZ (52)	36:16	30.1 (9.6)	N=90 48:42	27.43 (10.33)	Total brain volume cerebrospinal fluid (CSF), and CSF within the ventricular system. Regional measures: frontal, temporal, parietal, and occipital lobes and the cerebellum	MRI Automated volumetric measures using locally developed software	Men have brain tissue deficit in all four of the cortical brain tissue regions. Women have a deficit only in frontal tissue.
Andreasen et al 1990.	SZ (54)	36:18	M=32.46 (8.59) F=35.39 (10.75)	N=47 28:19	M 32.93 (9.25) F 36.63 (12.67)	Ventricular volume	MRI Manual measurement	Most of the increased ventricular size was found in the male patients. Significantly smaller thalamus in the male patients,

Reite et al 1997.	SZP (20)	11:9	M 37.1 (4.7) F 38.2 (5.6)	N=20 10:10	M 38.2 (9.3) F 3.1 (6.5)	Total brain volume, left and right hemisphere, and left and right superior temporal gyri.	MRI Combined automated and manual segmentation	Male patients showed less asymmetry than the control group, while the female patient showed significantly more asymmetry. The male patient had smaller superior temporal gyri than the control group. No evidence of total brain volume differences was observed.
Gur et al., 2000	SZ (70)	40:30	28.7 (6.9)	N=81 34:47	26.4 (6.7)	Gray and white matter volumes of the dorsolateral, dorsomedial, orbitolateral, and orbitomedial prefrontal cortex	MRI Manual segmentation	Reduction in the dorsolateral area in men (9%) and women (11%), for the dorsomedial area only in men (9%), and for orbital regions only in women (23% and 10% for lateral and medial, respectively). Schizophrenia is associated with reduced gray matter volume in prefrontal cortex, which affects men and women in the dorsolateral sector. The effects are moderated by sex for dorsomedial and orbital regions and are related

								to symptom severity and cognitive function.
Gur et al., 2000	SZ (100)	58:42	29.2 (7.3)	N=110 51:59	26.1 (6.3)	Gray and white matter volumes of temporolimbic (hippocampus and amygdala) and neocortical regions (superior temporal gyrus and temporal pole) were examined	MRI	Hippocampal: volume was reduced more in men (7%) than women (8.5%). Amygdala: more decreased volume in men while women had increased volume. temporal pole: more decreased gray matter in men (10%) than women (8.5%). Superior temporal gyrus, decrease only in men.
Lewine et al. 1995.	SZ (108), SZA (20), MDD (27), BPD (20)	SZ (82:26) SZA (7:13) MDD (7:20) BPD (5:15)	M 32.4 F 33.9 M 39.4 F 39.6 M 39.3 F41.4 M 32.6 F 39.7	N=150 59:91	M 31.5 F 35.2	Global	MRI Brain images evaluated by neuroradiologiste blind to diagnosis	SZ males had Significantly more morphologic anomalies especially of the lateral ventricles than healthy male volunteers. No difference in SZ women
Nopoulos et al. 1997	SZ (80)	40:40	M 28.8 (7.3) F 27.4 (7.8)	80 matched for age and sex	M 28.4 (7.1) F 27.8 (7.6)	Ventricles, CSF and whole brain volumes	MRI Automated volumetric measures of major brain regions.	Male patients having significantly larger ventricles than male controls, female patients showing no significant enlargement in comparison with female controls. Other structures: Male and female patients with schizophrenia have the same

								pattern of structural brain abnormalities, but male patients appear to manifest greater severity, especially with regard to ventricular enlargement.
Bryant et al. 1999.	SZ	59 (36:23)	M 32.66 (5.53) F37.31 (5.09)	37 (19:18)	M 34.26 (6.65) F 33.33 (8.02)	temporal lobe: superior temporal gyrus, the amygdala/hippocampal complex, and the temporal lobe the prefrontal cortex and caudate	MRI Automated volumetric measure	Left temporal lobe volume on the left was significantly smaller in male patients than in male comparison subjects. Female patients and female comparison subjects demonstrated no significant difference in temporal lobe volume. There were no statistically significant gender interactions for the superior temporal gyrus, the amygdala/hippocampal complex, or the comparison regions.
Flaum et al. 1995.	SZ	102 (70:32)		87		Lateral and third ventricles, thalamus, hippocampus, and superior temporal, caudate nuclei	MRI Regions of interest volume were outlined manually by an experienced technician on all slices in which they were visualized.	no significant Gender by Diagnosis effects for any of the regions of interest
Lauriello et al. 1997	SZ (23)	18:19	M 37.9 (9.2) F 39.8 (10.2)	N=23 18:19	M 38.4 (9.5) F 37.9 (9.2)	measures of head	MRI Volumetric semiautomated image analysis technique	There were no group-by-sex interactions.

						size, cortical gray matter, white matter and sulci, and lateral and third ventricles		No difference in ventricular enlargements and relation with age at symptom onset or length of illness in either men or women with schizophrenia
Narr et al.2004.	FES (50)	33:17	25.5 (4.5)	N=50 33: 17	27.8 (7.3)	Superior frontal (dorsolateral), inferior frontal (orbitofrontal), temporal, parietal and occipital.	MRI 3D gyral complexity Semi-automated and manual outlining	Significant increases in cortical folding in the right superior frontal cortex in male patients compared to controls, while no differences were observed in women
Narr et al. 2006	FES 72	51:21	25.1 (4.7)	N=78 37:41	27.3 (6.6)	Regional CSF volume	Measuring volumes of lateral ventricle horn and regional differences identified by comparing the distances from the ventricular surfaces to the central core at anatomically matched locations.	Dorsal superior horn expansions in female patients compared with same-sex controls.
Narr et al. 2003.	SZ (25)	15:10	M 32.4 (7.9) F 39.9 (10.2)	N=28 15:13	M 33.0 (10.1) F 35.2 (9.0)	Grey matter, white matter and CSF	MRI manual and automated measures	Greater abnormalities in male patients compared to female patients where specific increases in the sulcal and subarachnoid CSF that appeared prematurely in men diagnosed with schizophrenia, while women patients showed normal aging effects
Narr et al. 2000.	SZ (25)	15:10	31.1 (5.6)	N=28 15:13	30.5 (8.7)	Corpus callusum	MRI	Abnormalities in men patients compared to women patients.

							Manual contouring by diagnosis blind technician, and automated surface measure	Significant increases in maximum width in anterior and posterior regions in male patients compared to control men. Increased patterns of callosal variability in female patients but no effect of diagnosis between female groups.
Narr et al. 2005.	FES (72)	51:21	25.1 (4.7)	N=78 37:41	27.3 (6.6)	Whole brain and ROI	MRI Manual derived sulcal/gyral curves as landmarks Automated cortical pattern and grey matter thickness measures	Greater Loss of superior temporal sulcal slope asymmetry in the right hemisphere in male patients Female patients showed cortical thinning in cingulate and occipital regions bilaterally compared to healthy females, more widespread in right cingulate and left occipital cortex. Male patients showed thinning more prominently in the left hemisphere in caudal anterior cingulate cortices, within the paracentral lobule and posterior occipital regions bilaterally compared to healthy males. Male patients showed small regional thickness increases in

								the vicinity of the gyrus rectus compared to male controls. Cortical thinning in caudal anterior and posterior cingulate cortices (right hemisphere pronounced) and the cuneus was observed in female patients compared to same sex controls. Male patients showed thinning in the paracentral lobule and caudal anterior cingulate (left hemisphere pronounced) and posterior occipital cortices
Narr et al 2001.	SZ (25)	15:10	31.1 (5.6)	28 15:13	30.5 (8.7)	superior frontal (dorsolateral), parieto-occipital, temporal, and inferior frontal (orbitofrontal	MRI Manual and automated measures	Schizophrenia males show greater loss of superior temporal sulcal slope asymmetry (normally found healthy males) in the right hemisphere relative to schizophrenia females Greater variability in the longitudinal fissure, reflecting both larger sulci and larger cerebrospinal fluid (CSF) volume in males relative to female patients.
Molina et al 2005.	SZ (85) M: SZP N=51	59:29	M 27.2 (8.9) F 31.1 (10.3)	N=45 24: 21	M 31.2 (10.1) F 32.7 (13.0)	cortical prefrontal,	MRI Automated calculation of CSF	Men showed significantly more CSF in the left prefrontal area,

	SZU N=8 Females N=24 SZ paranoid N= SZ undifferentiated					temporal, and hemispheric CSF values		due to probable grey matter loss. CFS values in the prefrontal and temporal regions were positively correlated with illness duration in men, but not in women.
Yotsutsuji et al 2003.	SZ (40)	20:20	26.1 (5.0)	N=40 (20:20)	25.1 (5.8)	Perigenual cingulate gyrus	MRI Volumetric measure of both gray and white matter. Semi-automatic segmentation into gray matter, white matter, and cerebrospinal fluid. Perigenual cingulate gyrus volume done by one rater who was blinded to subjects' identity, gender, and diagnosis	Total (left and right) perigenual cingulate gray matter volume was significantly reduced in female schizophrenia patients compared with female controls. There was no significant difference in the gray matter volume of the perigenual cingulate gyrus between male groups. Significant gender differences were found in the total gray and white matter volume of the perigenual cingulate gyrus in control subjects (women _ men), although these gender differences were not significant in the patient group. Male patients had significantly increase volumes in the left temporal horn, bilateral anterior

								horns, the right body, as well as the third ventricle. Women patients showed similar, but less pronounced ventricular enlargements
Frederikse et al. 2000.	SZ (30)	15:15	M 39.00 (9.26) F 40.00 (10.51)	N=30 15:15	M 39.67 (11.06) F 38.40 (9.80)	inferior parietal lobule	MRI GM volume Semiautomatic into gray matter, white matter, and cerebrospinal fluid manual measure of inferior parietal lobule	Men with schizophrenia had a reversal of the normal asymmetry (i.e., they had right-greater-than-left IPL), as well as significantly decreased left IPL volume compared to control men. No significant differences in asymmetry or volume were observed in women patient relative to the same-sex controls Male patients exhibited a reversal of the normal left-greater-than-right male asymmetry in this region and had left inferior parietal lobule gray matter volumes that were significantly smaller than those of healthy male subjects. Female patients did not differ significantly from healthy female subjects in left or right

								inferior parietal lobule volume or in asymmetry.
Collinson et al. 2003.	EOSZ (33)	22:11	Total 16.8 (1.4) M 16.8 (1.3) F 16.8 (1.5)	N=30 18:12	Total=16.4 (1.7) M 16.3 (1.6) F 16.4 (1.9)	Left and right hemisphere volume	MRI Automated and manual segmentation	Male, but not female, patients had reduced left hemisphere volume and a trend to reduced temporal lobe volume. Reversal of normal rightward asymmetry in the female control group was reversed to a leftward asymmetry in females with schizophrenia.
Savadjiev et al. 2014.	AOSZ (39)	22:17	M 16.5 (0.97) F16.0 (1.0)	N=33 16:17	M 15.7 (1.5) F 15.2 (1.1)	the geometry of interhemispheric white matter connections	MRI DTI automated measures	Reversal of normal asymmetry where female patients showed asymmetry. These abnormalities were correlated with negative symptom severity in a sex-specific manner
Vogeley et al., 2000.	SZ (24)	11:13	M 51.27 5.44 F 55.85 8.90	N=24 11:13	Age at death M 54.18 (9.10) F 52.23 (13.56)	prefrontal regions	Post mortem planimetric analysis Gyrification index A gray-to-white-matter ratio and an asymmetry coefficient computation	Significant diagnosis-by-sex interaction in the right prefrontal cortex, where male patients had higher gyrification index (GI) in comparison to healthy men, while no significant differences were observed between two female groups
Mancini-Marïe et al., 2015	SZ (48)	24:24	M 31.25 (7.96) F 33.04 (8.38)	N=48 24:24	M 33.50 (8.69) F 29.92 (7.15)	Left and right hemispheres. Frontal, temporal, parietal, occipital cortex	MRI Automated gyrification index	significantly lower values of the GI in the right hemisphere in men with schizophrenia compared to the same-sex controls and no differences between women groups

								Greater decrease in hemispheric GI values in men patients Significant GI values decrease with the duration of illness in schizophrenia men but not in schizophrenia women Sex-by-illness duration interaction, such that men patients showed more rapid decrease in the right parietal and occipital GI, while women showed more rapid decrease in the left frontal and right temporal GI
Gur et al., 2002.	SZ (100)	58:42	29.2 (7.3)	N=110 51:59	26.1 (6.3)	Temporolimbic (hippocampus and amygdala) and neocortical regions (superior temporal gyrus and temporal pole)	MRI Grey and white matter volumes	Hippocampal gray matter volume was reduced in men (7%) and women (8.5%) with schizophrenia. Amygdala showed decreased volume was evident for men (8%) whereas women (10.5%) had increased volume. Temporal pole showed decreased gray matter in men (10%) and women (8.5%).

								Superior temporal gyrus, the decrease exceeded that of whole-brain only in men (11.5%). Cortical volumes were associated with better memory performance in healthy women.
Niu et al. 2004	SZ (40)	20:20	M 26.4 (5.1) F 25.9 (5.19)	N=40 20:20	M 25.5(5.6) F 24.8 (6.2)	Amygdala and the temporal lobe	MRI Semi-automated and manual volumetric measure	Only male patients had significantly reduced volumes in the bilateral amygdala relative to the same-sex controls. Significant left-smaller-than-right volumetric asymmetry of the amygdala was detected only in men and not in women with schizophrenia
Takayanagi et al. 2011	FES (52)	29:23	M 27.8 (6.0) F 28.1 (5.8)	N=40 (22:18)	M 29.9 (5.6) F 27.5 (4.8)	All regions ROI: hippocampus and amygdala	MRI Multiple brain measures (volume and cortical thickness) Fully automated procedure	Sex differences were found in the bilateral amygdala, with more reductions in men than women with schizophrenia
Irle et al. 2011.	SZ (46)	23:23	M 32.8(8.9) F33.4 (8.2)	N=46 23:23	M 33.22 (8.4) F 34.0 (8.6)	hippocampus	MRI Automated and manual tracing	Only men with schizophrenia had hippocampal volume reductions relative to the same-sex controls at the illness onset, but with longer illness duration women had similarly reduced hippocampal size as male patients.

								Only women patients showed an inverse relationship between the hippocampal volume and illness duration.
Goldstein et al. 2002	SZ (40)	27:13	M 46.6 (11.4) F 41.4 (7.0)	N=48 27:21	M 41.6 (11.6 F 39.0 (9.9)	Middle frontal gyrus, frontomedial and fronto-orbital cortices; basal forebrain, anterior, posterior and paracentral gyri, insula, parahippocampus gyrus, posterior parietal, primary auditory cortex, amygdala, hippocampus, dorsal medial thalamic nuclei, caudate, putamen, globus pallidum	MRI Semi-automated and manual volume measure	Volume reductions in ACC in women but not in men with schizophrenia, relative to the same-sex control Reversed sexual dimorphism where male patients showed greater grey matter volume of ACC than men.
Takahashi, et al. 2002	SZ (40)	20:20	M 26.4 (5.1) F 25.9 (5.1)	N=40 20:20	M 25.5 (5.9) F 24.8 (6.2)	Anterior cingulate gyrus	MRI Volume of the whole brain and both grey and white matter. All measurements were carried out by one rater, blinded to gender and diagnosis.	Volume reductions in ACC in women but not in men with schizophrenia, relative to the same-sex controls The right anterior cingulate was significantly reduced only in women with schizophrenia.

								Women patients lacked the normal structural asymmetry - right larger than left ACC. Contrary to prediction that men with schizophrenia would show more laterality disruption, they did not differ from the same-sex control group on any measure
Takahashi et al. 2004	SZT (26) SZ (58)	SZT 14:12 SZ 31:27	SZT M 23.6 (5.4) F 26.3 (4.6) SZ M 25.5 (4.9) F 26.2 (4.8)	N=61 31:31	M 24.9 (5.1) F 24.2 (5.9)	perigenual cingulate gyrus	MRI Volume of the gray and white matter All measurements were carried out by one rater, blinded to gender and diagnosis.	Schizophrenia patients showed a lack of normal gender differences of the perigenual cingulate gray matter seen in the healthy controls (females>males).
Takahashi et al. 2003	SZ (40)	20:20	26.1 (5.0)	N=40 20:20	25.1 (5.8)	perigenual cingulate gyrus	MRI Volume of both gray and white matter of the perigenual cingulate gyrus All measurements were carried out by one rater, blinded to gender and diagnosis.	Significant sex difference in the perigenual cingulate gyrus in control subjects where women had larger grey matter volumes than men. This difference was not significant in schizophrenia due to reduction in bilateral perigenual cingulate gray matter in female patients compared with female controls and no differences between the men groups.
Goldstein et al. 2007	SZ (88)	M 67.1% F 32.9%	44.6 (9.7)	N=48 M 56% F44%	40.5 (10.8)	Hypothalamus	MRI Segmentation hypothalamus	Contrary to expectations, hypothalamic volumes in

								schizophrenia patients were significantly larger than those in normal controls. These abnormalities were also present in nonpsychotic relatives of schizophrenia patients; they were positively correlated with anxiety and were more pronounced in women
Duggal et al. 2005	FES (30)	15:15	M 31.4 (5.5) F 25.9 (8.7)	N=30	M 33.5 (7.0) F 26.5 (11.4)	Insula	MRI Manual tracing of insular volumes	Women with schizophrenia had significantly reduced right insular volume relative to healthy women, while there was no effect in men

M: males, F: females, SZ: schizophrenia, FES: First episode schizophrenia, MRI: magnetic resonance imaging, SZT: schizotypal disorder, BPD: Bipolar disorder, SZA: schizoaffective disorder, FEP: first episode psychosis, SZP: paranoid schizophrenia, MDD: major depressive disorder, ROI: region of interest, SZU: schizophrenia undifferentiated, AOSZ: adolescent onset schizophrenia, EOSZ: early onset schizophrenia

- **Table Y. Differences between ICD-10 and DSM-IV in schizophrenia**

	ICD-10	**DSM-IV**
Diagnoses	1 symptom from Schneiderian first rank or 2 from a second list of psychotic symptoms	1 symptom from Schneiderian first rank or 2 from a second list of psychotic symptoms
Symptoms	List 1) thought echo, thought insertion or withdrawal or thought broadcasting; delusions of control, influence or passivity; hallucinatory voices giving a running commentary or discussing the patient among themselves or persistent delusions of other kinds that are "completely impossible." List 2) hallucinations accompanied by delusions or overvalued ideas; incoherence or irrelevant speech; catatonic behavior; and "negative" symptoms.	List 1) bizarre delusions (which would cover the three delusional symptoms in the ICD-10 list) and auditory hallucinations List 2) 5 symptoms: delusions of any type; hallucinations of any type; disorganized speech; catatonic or grossly disorganized behavior, and negative symptoms.
Duration	Minimum 1 month	Minimum 1 month and at least 6 months for a diagnosis
Functioning	No specification	Since the onset of the illness functioning is markedly below that achieved prior to the onset.
Between episodes	Negative symptoms (or no symptoms) between episodes. These are further subtyped based on whether the negative symptoms are progressive or stable.	Characterized by the presence or absence of interepisode residuel symptoms which may be either negative symptoms or attenuated forms of the defining psychotic symptoms.

First onset of psychotic symptoms lasting for at least 1 month but less than 6	Diagnosed as Schizophrenia	Diagnosed as Schizophreniform Disorder.
F20.0 Paranoid Schizophrenia	Requires that the delusions or hallucinations be prominent whereas other specific symptoms (i.e., flattening or incongruity of affect, catatonic symptoms, or incoherent speech) must not "dominate the clinical picture."	Requires that the individual be *preoccupied* with one or more delusions or frequent hallucinations and that none of a list of different specific symptoms (i.e., disorganized speech, disorganized or catatonic behavior, or flat or inappropriate affect) be also prominent.
F20.1 Hebephrenic Schizophrenia (Disorganized Schizophrenia in DSM-IV)	Flat or inappropriate affect and either disorganized speech or disorganized behavior	Disorganized speech, disorganized behavior and flat or inappropriate affect are all required.
F20.2 Catatonic Schizophrenia The lists of catatonic symptoms share most features in common except for :	ICD-10 requires only one catatonic symptom lasting at least 2 weeks. Command automatism	The DSM-IV definition is more severe in that a minimum of two catatonic features must be present. Echolalia and echopraxia
F20.3 Undifferentiated Schizophrenia	Either having "insufficient symptoms" to meet the criteria for one of the other subtypes or "so many symptoms that the criteria for more than one of the other subtypes is met."	Only for cases that do not meet criteria for any of the other subtypes.

F20.5 Residual Schizophrenia	The ICD-10 definition requires that there be at least 12 months of negative symptoms (four drawn from a possible list of six) in an individual for whom the general criteria for Schizophrenia are not currently met.	The DSM-IV definition is more broadly defined in that the criteria also allow for two or more active phase symptoms to be present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences). DSM-IV also does not specify a duration.
F20.6 Simple Schizophrenia (Simple Deteriorative Disorder in DSM-IV)	Requires that there be a significant change "in the overall quality of some aspects of speech or personal behavior manifest as loss of drive or interests, aimlessness, idleness, a self-absorbed attitude and social withdrawal."	Not is DSM-IV, but under Simple Deteriorative Disorder Requires "poor interpersonal rapport, social isolation, or social withdrawal." Exclusion of Personality, Mood, or Anxiety Disorder.

- **Adapted from First MB (2009a, 2009b & 2007)(700, 701)**