FACULDADE DE MEDICINA DA UNIVERSIDADE DE COIMBRA

MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

DIOGO ALEXANDRE SANTOS PINTO

BRAIN HEMISPHERIC ASYMMETRY IN SCHIZOPHRENIA AND BIPOLAR DISORDER

ARTIGO CIENTÍFICO ORIGINAL

ÁREA CIENTÍFICA DE PSIQUIATRIA

Trabalho realizado sob a orientação de:

NUNO GONÇALO GOMES FERNANDES MADEIRA

JOÃO VALENTE DUARTE

ABRIL/2023

BRAIN HEMISPHERIC ASYMMETRY IN SCHIZOPHRENIA AND BIPOLAR DISORDER

Diogo Pinto[1]; Ricardo Martins[1,2]; António Macedo[2,3,4]; Miguel Castelo Branco[1,2]; João Valente Duarte[1,2,(*)]; Nuno Madeira[2,3,4,(*),#]

1. Faculty of Medicine, University of Coimbra, Portugal
2. Coimbra Institute for Biomedical Imaging and Translational Research (CIBIT), Institute of Nuclear Sciences Applied to Health (ICNAS), University of Coimbra, Portugal
3. Department of Psychiatry, Centro Hospitalar e Universitário de Coimbra (CHUC), Coimbra, Portugal
4. Institute of Psychological Medicine, Faculty of Medicine, University of Coimbra, Portugal

(*) These authors contributed equally to this work.

Corresponding author at: CIBIT, ICNAS-Instituto de Ciências Nucleares Aplicadas à Saúde, Pólo das Ciências da Saúde, Universidade de Coimbra, Azinhaga de Santa Comba, 3000-548 Coimbra, Portugal

E-mail address: nmadeira@ucc.pt

TABLE OF CONTENTS

RESUMO

Objetivos

Este estudo teve como objetivo comparar a assimetria cerebral em doentes com esquizofrenia (ESQ), perturbação bipolar (PBP) e controlos saudáveis para avaliar se padrões de assimetria poderiam discriminar e estabelecer fronteiras entre duas doenças mentais graves com fenótipos parcialmente sobrepostos.

Métodos

Aplicámos uma abordagem de morfometria baseada em voxel totalmente automatizada para avaliar a assimetria estrutural hemisférica do cérebro em imagens de ressonância magnética (RM) estrutural em 60 indivíduos dos três grupos (ESQ=20; PBP=20; controlos saudáveis=20), todos destros e emparelhados por género, idade e educação.

Resultados

Foram encontradas diferenças significativas na assimetria da substância cinzenta entre doentes com ESQ e PBP, entre doentes com ESQ e controlos saudáveis e doentes com PBP e controlos saudáveis. Encontrámos um índice de assimetria (IA) mais elevado em doentes com PBP quando comparados com ESQ nas áreas de Brodmann 6, 11 e 37 e no córtex cingulado anterior, e um IA mais elevado em doentes com ESQ quando comparados com PBP a nível do cerebelo.

Conclusões

O nosso estudo encontrou diferenças significativas na assimetria cerebral entre doentes com ESQ e PBP. Estes resultados promissores poderiam ser traduzidos para a prática clínica, dado que, as alterações estruturais do cérebro detetadas pela RM, são bons candidatos para exploração como marcadores biológicos no diagnóstico diferencial, além de ajudar a compreender anomalias específicas destas doenças.

ABSTRACT

Objectives

This study aimed to compare brain asymmetry in patients with schizophrenia (SCZ), bipolar disorder (BPD), and healthy controls to test whether asymmetry patterns could discriminate and set boundaries between two partially overlapping severe mental disorders.

Methods

We applied a fully automated voxel-based morphometry (VBM) approach to assessing structural brain hemispheric asymmetry in magnetic resonance imaging (MRI) anatomical scans in 60 participants (SCZ=20; BPD=20; healthy controls = 20), all right-handed and matched for gender, age, and education.

Results

Significant differences in grey matter asymmetry were found between patients with SCZ and BPD, between SCZ patients and healthy controls (HC) and between BPD patients and HC. We found a higher asymmetry index (AI) in BPD patients when compared to SCZ in Brodmann areas 6, 11, and 37 and anterior cingulate cortex, and an AI higher in SCZ patients when compared to BPD in the cerebellum.

Conclusion

Our study found significant differences in brain asymmetry between patients with SCZ and BPD. These promising results could be translated to clinical practice, given structural brain changes detected by MRI are good candidates for exploration as biological markers for differential diagnosis, besides helping to understand disease-specific abnormalities.

PALAVRAS-CHAVE

Esquizofrenia; Doença Bipolar; Assimetria Hemisférica; Imagiologia por Ressonância Magnética

KEYWORDS

Schizophrenia; Bipolar Disorder; Hemispheric Asymmetry; Magnetic Resonance Imaging

ABBREVIATIONS

ACC	Anterior Cingulate Cortex
AI	Asymmetry Index
AP	Antipsychotic
BA6	Brodmann Area 6
BA11	Brodmann Area 11
BA25	Brodmann Area 25
BA32	Brodmann Area 32
BA37	Brodmann Area 37
BPD	Bipolar Disorder
BPRS	Brief Psychiatric Rating Scale
CPZE	Chlorpromazine equivalents
FWHM	Full-width at Half Maximum
GM	Grey Matter
HC	Healthy Controls
ITAQ	Insight and Treatment Attitudes Questionnaires
MD	Mood Stabilizing
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
SCZ	Schizophrenia
SD	Standard Deviation
SP	Personal and Social Performance Scale
SPM	Statistical Parametric Mapping
VBM	Voxel-Based Morphometry
WM	White Matter

INTRODUCTION

Schizophrenia (SCZ) is characterized by positive psychotic symptoms (hallucinations, delusions, formal thought disorder), negative symptoms (flat affect, poor motivation, avolition) and, in many cases, social and occupational decline that can lead to life-changing consequences even in those who have good outcomes. (1,2)

Bipolar Disorder (BPD) is a mood disorder commonly characterized by nonspecific symptoms, mood lability, or a depressive episode. BPD can be defined by episodes of mania (BPD type 1) or characterized by at least one hypomanic episode and one major depressive episode (BPD type 2). Common symptoms during manic episodes are grandiosity, hyperactivity, psychotic symptoms and expansive mood, whereas through depressive episodes are sadness, decreased energy and social withdrawal. (3)

Furthermore, BPD can be easily confused with SCZ, particularly when psychotic symptoms are prominent due to overlap in clinical presentation. (4–6) In addition, treatment options are highly different for both pathologies and might impact mortality and morbidity, so it is crucial to define biomarkers, especially from the earliest stages of the diseases, that can help differentiate each pathology. (4) Once several studies have described a high genetic overlap between SCZ and BPD (4,5,7) and specific biomarkers for BPD are not yet available, (3) structural brain changes detected by magnetic resonance imaging (MRI) are good candidates for exploration as biological markers to distinguish both conditions. (7)

Left-right hemispheric asymmetry is an important aspect of human brain organization for diverse cognitive functions such as language, social cognition and executive and affective processes. Hemispheric asymmetry can be altered in various aspects such as anatomical grey and white matter measures, functional and structural connectivity, behavioral associations and gyrification. (8) Whereas some studies found that differences in SCZ are more evident in the left hemisphere, while changes in BPD are more significant in the right hemisphere, (7) others have provided evidence of common abnormalities in brain structures in patients with SCZ and BPD. (5)

Global grey matter (GM) asymmetry is related to developmental stability and is a useful indicator of perturbations during neurodevelopment. In addition, global GM asymmetry was associated with avolition and anxiety, however, other symptoms like hallucinations were not. (9) Structural brain modifications and disrupted interregional connections have been related to many characteristic symptoms and cognitive impairment demonstrated in patients with SCZ. (10)

It is widely described by evidence that there is atypical lateralization in brain structure, cortical thickness and brain volumetric asymmetries in SCZ and BPD either *post-mortem* or in neuroimaging investigations, which proposes that both pathologies may be the result of a failure of the normal lateralization process of the brain. However, GM volume reductions are consistently more extensive in SCZ, except in BPD patients with comorbid psychosis. (4,5,9,11,12) Diverse studies reported that patients with either pathology have more global GM asymmetry than healthy controls (HC) with reduced cortical volume and thickness. Cortical volume variations in SCZ are explained by changes in cortical thickness and surface area, while in BPD, they are mostly justified by cortical thinning. (4,9,13–15) It is also important noting that no differences were detected in cortex thickness and surface area between patients with BPD type 1 and type 2. (15) It is important to take into account that cortical thickness in SCZ in prefrontal and temporal cortical areas are modulated by antipsychotic (AP) treatment and illness duration. (4)

Brain changes with extensive GM loss in SCZ patients when compared to BPD patients include neocortical structures (prefrontal and temporal cortices), limbic (amygdala, hippocampus, thalamus), paralimbic (anterior cingulate, insula) and in some degree, the cerebellum and increased GM volume in basal ganglia (globus pallidus) in SCZ but not in BPD. While changes in BPD are more restricted to paralimbic regions, frontal cortex and thalamus, areas involved in reward and pain systems and emotional regulation. (1,4,7,11–14,16–19) Despite SCZ presented GM volume deficits in multiple cortical and subcortical areas, (10) patients with SCZ, compared with HC, show more symmetry in subcortical areas such as caudate nucleus and hippocampus, except the thalamus and HC seem to be more symmetric in cortical areas such as prefrontal region and insula. (9)

Enumerating other changes that could contribute to brain hemispheric asymmetry, although anatomical brain changes affect GM more than white matter (WM), WM connectivity dysfunctions are also present in SCZ and BPD (5) in alignment with GM variations and influence connectivity in prefrontal and limbic regions in SCZ. (11)

Regarding the gyrification index, studies describe divergent gyrification of the left supramarginal gyrus with increased gyrification in BPD and reduced gyrification in SCZ, and decreased gyrification of the right inferior frontal gyrus in SCZ. (4)

Taking all previous studies and knowledge into consideration and exploring the lack of studies directly comparing hemispheric asymmetry in SCZ and BPD, our main purpose was to directly compare carefully defined matched groups of SCZ vs BPD patients and

HC to find possible structural asymmetry-based biomarkers that can help differential diagnosis between pathologies and guide future research.

METHODS AND MATERIALS

Participants

This study aimed to compare brain MRI scans of individuals with SCZ (n=20), BPD (n=20) and HC (n=20), all right-handed and matched for age (18-54), gender and education. Participants were recruited from a major university hospital, and inclusion criteria for clinical groups were: a) ICD-10 criteria for SCZ or BPD confirmed through a direct interview by an experienced psychiatrist and medical records reviewing; b) capacity to consent; c) age between 18–54; d) right-handedness through evaluation with the Edinburgh Handedness Inventory; (20) e) clinical stability in the last 3 months prior to enrolment with unchanged medication for a similar period. Exclusion criteria were: a) neurological or medical comorbidity (e.g. head trauma, epilepsy, neurodevelopmental disorders); b) MRI contra-indications; c) substance abuse/dependence. Patients' clinical assessment included the following instruments: the Schizo-Bipolar Scale, (21) developed to capture the dimensional interaction between affective symptoms and psychosis; the Insight and Treatment Attitudes Questionnaire (ITAQ), to assess insight; (22) the Personal and Social Performance Scale (PSP), (23) addressing functioning; and the Brief Psychiatric Rating Scale (BPRS), (24) for general psychopathology assessment. Current AP exposure in SCZ and BPD patients was calculated through chlorpromazine equivalents (CPZE). (25) Control individuals matched for age, gender and education were recruited from the institution's workers and their relatives with a brief interview excluding personal or first-degree family history of mental disorders, namely SCZ or BPD, in addition to general exclusion criteria. The study was approved by the local Ethics Committee of the Faculty of Medicine of the University of Coimbra (ref. CE-010/2014), conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

MRI Acquisition

MRI data were collected with a Siemens Magnetom TIM Trio 3T scanner (Siemens, Munich, Germany) with a phased array 12-channel birdcage head coil. The MRI dataset consisted of a 3D anatomical T1-weighted MPRAGE (magnetization-prepared rapid gradient echo) pulse sequence (TR 2530 ms; TE 3.42 ms; TI 1100 ms; flip angle 7º; 176 single-shot interleaved slices [no inter-slice gap] with isotropic voxel size 1x1x1mm; FOV 256 mm) of all 60 participants.

Processing and Asymmetry Index

The data were processed and analyzed using a recently published protocol - "A 12-step user guide for analyzing voxel-wise grey matter asymmetries in statistical parametric mapping" - to find out biomarkers that can help in the differential diagnosis. (26) This protocol describes a fully automated voxel-based morphometry (VBM) approach to assess structural brain hemispheric asymmetry, which is capable of capturing GM asymmetries with extremely high regional specificity. (26,27)

All images were processed and analyzed using SPM8 and VBM8 toolbox. We performed tissue segmentation into three voxel classes (GM, WM and cerebrospinal fluid) and we flipped tissue segments at midline. We also performed spatial normalization using DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra) approach. DARTEL is a high-dimensional normalization algorithm, provided by SPM8, that has been shown to secure a better registration across brains than the Statistical Parametric Mapping (SPM) default normalization, (28) because asymmetry VBM needs an accurate voxel-wise correspondence not only between brains, used in standard VBM, but also across hemispheres. Then we warped the original and flipped tissue segments to the symmetric DARTEL template. Combined with a right hemisphere mask, we calculated the AI images and discarded the left hemisphere. To control the possible impact of noise, spatial smoothing was also implemented with a size of the smoothing kernel of 8 8 8 mm full-width at half maximum (FWHM). Spatial smoothing certifies that random errors have a Gaussian distribution (a precondition for parametric tests). Processing also included quality assurance since all images were visually inspected before and during pre-processing to guarantee that no parts of the brain were cut-off, wrapped or distorted, and that images have no artifacts. Finally, the asymmetry index (AI) was quantified in each voxel by comparing original and flipped GM segments using the following equation:

$$Asymmetry\ Index = \frac{(original - flipped)}{0.5 \times (original + flipped)} \quad (1)$$

Statistical Analysis

We performed statistical analyses in SPM8 statistical module applying a two-sample t-student test, to assess differences in GM asymmetry between the group of patients with SCZ and the group with BPD, between each group of patients individually and HC. The spatially normalized and smoothed GM segments constitutes the input for the voxel-wise statistical analyses. (29) We tested group differences and considered differences significant at a voxel-level threshold of $p<0.001$. A positive AI indicates rightward

asymmetry, whereas a negative AI indicates leftward asymmetry, with higher absolute values reflecting stronger asymmetry. (26) An independent samples t-test between SCZ and BPD patients' left and right hemispheres volumes in significant clusters to found whereas the volume differences in one hemisphere is different between SCZ and BPD patients was also performed.

Clusters with significant differences in GM asymmetry index were labelled according to their MNI coordinates and the corresponding anatomical area of the brain using the software package GingerALE (version 3.0.2; http://www.brainmap.org/ale/).

RESULTS

Demographic and Clinical Characterization

Clinical and demographic data of the study participants are summarized in table 1. All patients with SCZ were on AP medication, mostly atypical APs: first-generation AP (n=2), one second-generation AP (n=16) and a combination of two second-generation AP (n=2). Among the patients with BPD, most (n=18) were on regular mood stabilizing (MD) medication: MD monotherapy (n=7), MD in association (n=1), MD and atypical AP (n=4), monotherapy with atypical AP (n=4) and a combination of atypical AP (n=2). One patient was medicated with lithium and two were stable without medication.

Groups were balanced for age and gender, with exactly the same within-group distribution (x^2=0.000, p=1.000). SCZ and BPD groups had no relevant clinical or demographic differences besides AP exposure, higher in SCZ patients (p=0.032). Concerning psychopathological evaluation, SCZ patients had superior (p<0.001) general psychopathologic scores and worse (p=0.001) functioning than BPD patients. Individuals in both clinical groups were either in remission or sustained clinical stability, as shown by mean BPRS scores for patients with SCZ (35.65±6.41) and BPD (29.11±2.61). Differences between the two groups were statistically significant (p<.001). SCZ patients had lower social functioning than BPD patients using PSP scores (p=.001). BPD group had higher (p= 0.044) insight than SCZ patients. SCZ group had much higher scores (p< 0.001) on the Schizo-Bipolar Scale than BPD group as expected, because higher scores are associated with prototypical SCZ syndromes, whereas paradigmatic BPD patients score lower. (4)

Table 1 - Clinical and Demographic data of study groups

	Schizophrenia N=20	Bipolar Disorder N=20	Healthy Controls N=20	Test Statistics	p-value
Gender (Female | Male)	7 | 13	7 | 13	7 | 13	x^2 0.000	1.000
Age - years (SD)	31.5 (10.3)	31.65 (10.00)	31.5 (10.3)	F 0.001	.992
Education - years (SD)	13.6 (3.7)	13.85 (2.64)	14.9 (4.52)	F 0.756	.474
Age of disease onset - years (SD)	25.6 (6.9)	26.5 (8.8)	-	t -0.276	.784
Duration of disease - years (SD)	6.0 (7.9)	5.2 (4.3)	-	t 0.297	.769
Number of lifetime admissions (min - max)	1.25 (0-7)	1.25 (0-4)	-	t 0.000	1.000
Antipsychotic exposure (CPZE) - mg (SD)	380.0 (337.3)	160.8 (272.3)	-	t 2.226	.032
History of psychotic symptoms	20	16	-	x^2 0.035	.106
History of substance abuse	5	7	-	x^2 0.557	.731
History of suicidal behaviours	4	4	-	x^2 0.000	1.000
Psychopathology - BPRS (SD)	35.65 (6.41)	29.11 (2.61)	-	t 3.991	.000
Functioning - PSP (SD)	80.22 (12.36)	92.00 (4.00)	-	t -3.845	.001
Insight - ITAQ (SD)	17.12 (3.16)	19.13 (2.22)	-	t -2.100	.044
Scizo-Bipolar Scale (min – max)	8.00 (7-9)	0.94 (0-2)	-	t 28.356	.000

BPRS – Brief Psychiatric Rating Scale; CPZE – Chlorpromazine equivalents; ITAQ – Insight and Treatment Attitudes Questionnaires; PSP – Personal and Social Performance Scale; SD – Standard Deviation

Voxel-based Morphometry – Asymmetry Index SCZ vs BPD

The contrast of higher GM asymmetry index in SCZ compared with BPD, performed at the whole brain level, revealed a significant group difference ($p<0.001$) in one cluster with a cluster size of 82 voxels, at the MNI coordinates (11,-34,-26) and (6,-45,-30), corresponding to right cerebellar hemisphere, anterior lobe, *gyrus culmen*. The analysis of the cluster specific mean AI revealed a stronger rightward asymmetry in the SCZ group than in the BPD group. The analysis between SCZ and BPD groups of this cluster's specific GM volume showed that although not statistically significant ($p=0.079$), there is a trend to SCZ group have lower GM volume in the left hemisphere. No statistically significant differences were found in the right hemisphere ($p=0.406$) These results are described in figure 1, table 2 and table 3.

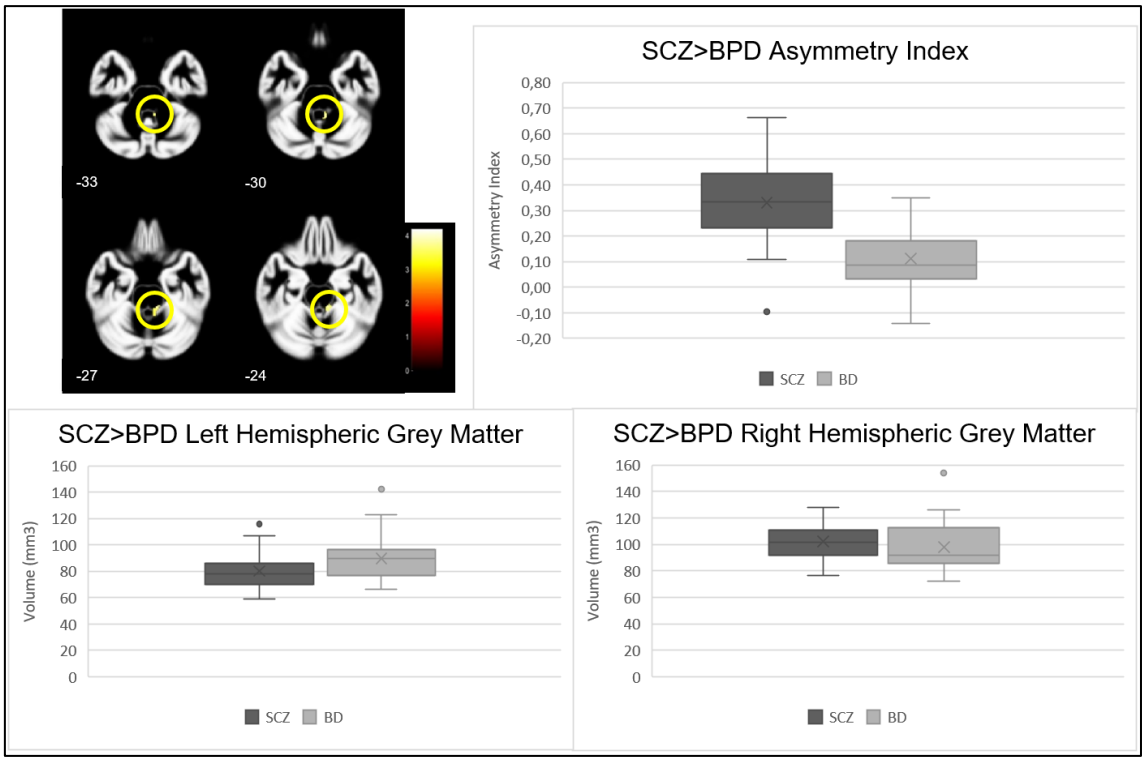

Figure 1 – Location, Asymmetry Index and Left and Right GM Volumes in clusters showing a significant contrast SCZ>BPD.

The contrast of higher GM asymmetry index in BPD compared to SCZ, performed at the whole brain level, revealed significant group differences ($p<0.001$) in four clusters described in figure 2 and table 2. The evaluation of each cluster's specific mean AI revealed a stronger rightward asymmetry in the BPD group in all clusters. The analysis between SCZ and BPD groups GM's volume showed that SCZ group had statistically significant higher GM volume in the left hemisphere in Brodmann area 6 (BA6) ($p=0.011$) and Brodmann area 11 (BA11) and anterior cingulate cortex (ACC) ($p=0.016$). While BPD group had statistically significant, or a tendency to, higher GM volume in the right hemisphere in BA6 ($p=0.009$ and $p=0.071$), in Brodmann area 37 (BA37) ($p=0.009$) and in BA11 and ACC ($p=0.052$). These GM volume differences are described in table 3.

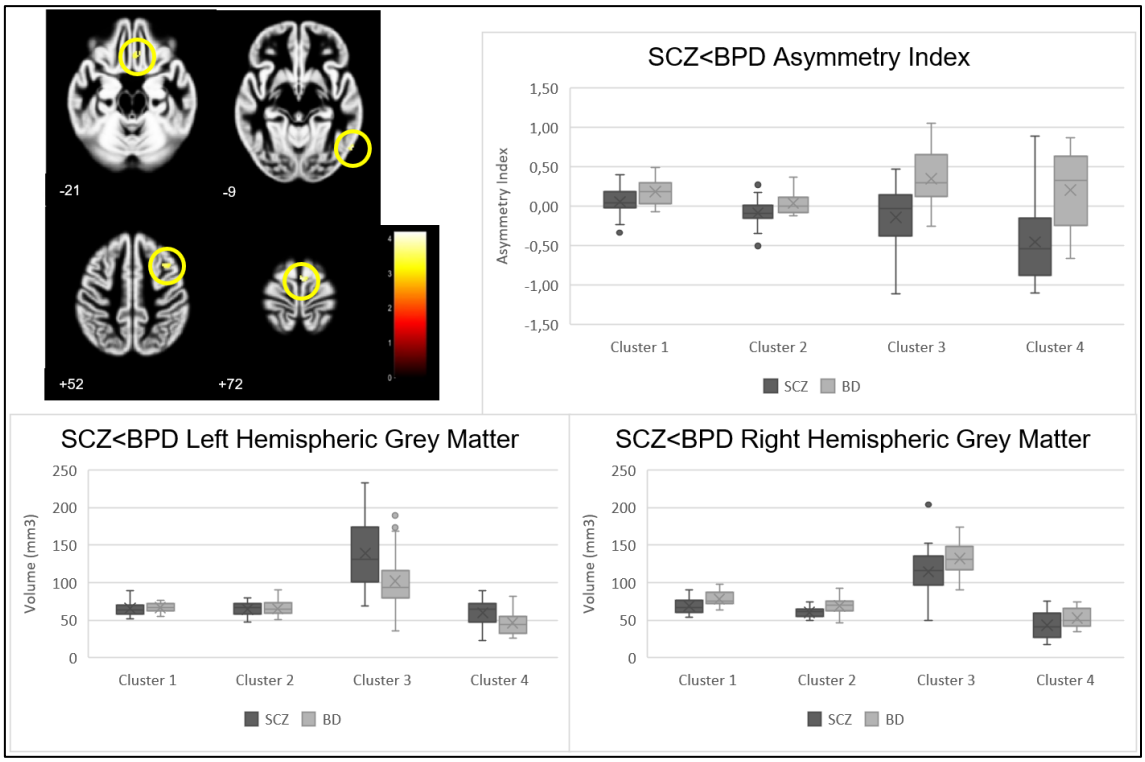

Figure 2 – Location, Asymmetry Index and Left and Right GM Volumes in clusters showing a significant contrast SCZ<BPD.

Voxel-based Morphometry – Asymmetry Index SCZ vs HC and BPD vs HC

We performed, at a whole brain level, two sample t-student tests of the hypotheses SCZ>HC, SCZ<HC, BPD>HC and BPD<HC. Table 2 describes all clusters showing significant group differences in voxel-wise GM asymmetry.

Table 2 – Clusters' Description – Significant GM Asymmetries between SCZ vs BPD, SCZ vs HC and BPD vs HC and respective Cluster Size, MNI coordinates and corresponding Brain region

	Cluster	p-value	Z statistic	Cluster size	MNI coordinates (X, Y, Z)	Brain region
SCZ>BPD	1	<0.001	3.78	82	(11,-34,-26)	Right Cerebellum hemisphere, Anterior Lobe, Gyrus Culmen
		<0.001	3.52		(6,-45,-30)	
SCZ<BPD	1	<0.001	3.92	38	(3,-6,72)	Right Cerebrum, Frontal Lobe, Medial Frontal Gyrus, Brodmann area 6
	2	<0.001	3.78	35	(57,-66,-9)	Right Cerebrum, Temporal Lobe, Fusiform, Inferior Temporal and Middle Temporal Gyrus, Brodmann area 37
	3	<0.001	3.47	60	(33,14,52)	Right Cerebrum, Frontal Lobe, Medial Frontal Gyrus, Brodmann area 6
	4	<0.001	3.44	33	(5,29,-21)	Right Cerebrum, Frontal and Limbic Lobe, Medial Frontal Gyrus and Anterior Cingulate Cortex, Brodmann area 11, 25 and 32
SCZ>HC	1	<0.001	4.37	207	(44,21,-9)	Right Cerebrum, Frontal Lobe, Inferior Frontal Gyrus, Brodmann area 47
		<0.001	3.82		(39,23,-17)	
	2	<0.001	3.56	57	(30,-21,74)	Right Cerebrum, Frontal Lobe, Precentral Gyrus, Brodmann area 4 and 3
SCZ<HC	1	<0.001	3.71	83	(35,-70,54)	Right Cerebrum, Parietal Lobe, Superior Parietal Lobule, Brodmann area 7
		<0.001	3.59		(29,-64.52)	
	2	<0.001	3.68	33	(17,11,10)	Right Cerebrum, Caudate Body
BPD>HC	1	<0.001	4.50	112	(47,23,9)	Right Cerebrum, Frontal Lobe, Sub-gyral, White Matter
	2	<0.001	4.43	81	(38,38,6)	Right Cerebrum, Frontal Lobe, Sub-gyral, White Matter
	3	<0.001	3.61	33	(15,11,-3)	Right Cerebrum, Caudate Head
BPD<HC	1	<0.001	4.29	45	(16,-60,60)	Right Cerebrum, Parietal Lobe, Precuneus, Brodmann area 7

Table 3 – Independent samples t-test between SCZ vs BPD patients' Left and Right Hemispheres Volumes in significant clusters

		p-value	
	Cluster	**Left Hemisphere**	**Right Hemisphere**
SCZ>BPD	1	0.079	0.406
SCZ<BPD	1	0.722	0.009
	2	0.903	0.001
	3	0.011	0.077
	4	0.016	0.052

DISCUSSION

To our knowledge, this study is the first to employ a standard protocol (26) to directly investigate differences in GM volume asymmetry in patients with SCZ and BPD in the same study. Our study found significant differences in GM asymmetry between patients with SCZ and BPD, as well as significant differences between SCZ patients and HC and between BPD patients and HC. Notably, the clusters with significant AI differences between each patient group and HC are different from the ones revealed when directly comparing SCZ and BPD, thus conferring discriminative specificity to these results and highlighting the potential of this measure of GM volume asymmetry to constitute a brain marker that might help in the differential diagnosis between these two archetypal psychiatric diseases.

The specific contrast of SCZ>BPD revealed that the AI is higher in the cerebellum in SCZ patients than in BPD patients indicating that SCZ patients had a stronger rightward asymmetry than BPD patients. Comparing SCZ and BPD groups, SCZ patients had lower volume in the left hemisphere. The cluster with a significant difference between patient groups corresponds to the *gyrus culmen* in the anterior lobe of the right cerebellar hemisphere. Although the evidence for cerebellar abnormalities in SCZ is getting stronger, it is less extensive than for other brain regions like frontal and temporal cortices. (17) However, in BPD, few studies demonstrate differences in cerebellum. Only recently, implicit motor sequence learning impairment, already shown in SCZ, was connected to cerebellar abnormalities in BPD. (30) The cerebellum has been historically considered to serve as a coordinator of motricity function, while SCZ has been considered a disorder that mainly affects the cerebrum. However, nowadays it is well-recognized that the cerebellum is connected to many cerebral cortical regions by a cortical-cerebellar-thalamic-cortical circuit and might play a crucial role in coordination and modulation of cortical activity. (17,31) The cerebellum innervates not only motor areas of the cortex, but also prefrontal and parietal cortices involved in cognition by connections via the thalamus. (2) It has been shown by functional magnetic resonance that the cerebellum is activated in various cognitive functions such as facial recognition, emotion attribution, attention, verbal and motor learning, sensory discrimination, complex problem solving, many types of memory (2,17,31) and visual perception, (32,33) both in health and disease. (34) Since the cerebellum plays an important role in so many cortical activities, cerebellar deficiency and a disturbed prefrontal-thalamic-cerebellar circuit could lead to cortical malfunction and contribute to the diversity of symptoms and cognitive dysfunctions observed in SCZ. (2,17,35) Abnormal posture and proprioception, impaired eyeblink conditioning and impaired adaptation of the vestibular ocular reflex and

neurological soft signs (poor motor coordination, sensory-perceptual difficulties, and involuntary movements), that appear in SCZ, are correlated with a decrease in GM volumes in cerebellum and related networks, shown on structural MRI. (31,36) Those structural deficits were also associated with negative symptoms. (37) GM volume in the left cerebellum negatively correlates with motor sequencing dysfunction on the neurological soft signs scale. (35) A recent study revealed that SCZ patients had unilateral disruptions of left cerebellar regions associated with motor learning. (30) SCZ patients have difficulty discriminating between the self and other individuals and identify whether their thoughts and actions are independent of external influences. That information is integrated by Purkinje cells which are decreased in size or density. These experiences may cause various symptoms, such as hallucinations, thought insertion and replaced control of will. (17,31) Our findings of left hemisphere GM volume decrease is thus in accordance with this literature. Nonetheless, further studies are needed to understand the impact of this finding on the differential diagnosis and the function of cerebellum in BPD's pathophysiology.

Regarding the hypothesis of higher GM volume asymmetry in BPD compared to SCZ (contrast SCZ<BPD), several clusters were found to have significant differences between groups. On the one hand, differences were found in two clusters corresponding to BA6, in the medial frontal gyrus of the right hemisphere. BA6 is composed by a lateral portion – premotor cortex, responsible for planning movements, correction of postural adjustments and locomotion and social cognition skills as part of the mirror neuron system (6,38) - and by a medial portion – supplementary motor cortex, responsible for planning, initiation, and anticipation of body movements. (38,39) BA6 plays an important role in working memory and attention (40) and language processing, all of which are disturbed in SCZ and BPD. (35) Our results support that BA6 had more AI in BPD patients than in SCZ patients, indicating that BPD patients had a stronger rightward asymmetry than SCZ patients. Comparing SCZ and BPD groups, BPD patients had higher GM volume in right hemisphere for both clusters and less GM volume in left hemisphere for cluster 3. Other studies support our results that SCZ patients had less GM in right BA 6, and BPD patients had higher volume, by direct comparison between SCZ and BPD patients. (7,41) Motor abnormalities are an overlapping symptom in SCZ and BPD, mainly in the form of neurological and cerebellar soft signs (similar disturbance between groups) and implicit motor learning disturbance and the expression of that common pattern of abnormality in these diseases seems to be related to a dysfunction in cortical-cerebellar-thalamic-cortical circuit. (35,39) The hypothesis that the right hemisphere may be dominant in mood regulation correlates with a right hemisphere

disturbance in BPD. The presence of left and right hemisphere disruptions, especially in supplementary motor cortex in mania may explain the coexisting affective and psychotic symptoms. (42) Morphological abnormalities in left supplementary motor cortex seem to predispose to develop disturbances of higher motor control during acute episodes of psychosis. (43) Supplementary motor cortex blood flow is increased in patients with periodic and current catatonia. In addition, the greater the tic severity, the bigger the functional alterations in premotor and prefrontal regions, encompassing the supplementary motor cortex and middle frontal gyrus. (39) BPD also has interhemispheric asymmetry of motor cortical excitability with lower excitability in the right hemisphere, when compared to the contralateral (44) and a reduced regional homogeneity in the left middle frontal gyrus. (45)

On the other hand, higher AI in BPD compared to SCZ was observed in a cluster corresponding to BA37, in the inferior temporal and middle temporal parts of the fusiform gyrus in the right hemisphere. The fusiform gyrus is a key region for language and emotional processing, regulation of responses during face recognition, processing of visual forms of language and verbal listening stimulus and is known to be disturbed in SCZ, contributing to the social deficits and severe cognitive of this disease. (46–50) The fusiform gyrus is interconnected with other language-processing areas in temporoparietal and frontal regions that support semantic language processing. (46) It also has connections with cerebellar regions and prefrontal cortex. (50) Our results support that BA37 had more AI in BPD patients than in SCZ patients, indicating that BPD patients had a stronger rightward asymmetry. Comparing SCZ and BPD groups, BPD patients had higher GM volume in right hemisphere. Knowledge about fusiform gyrus and differences between groups are heterogeneous in the literature, but dysfunction of this area and its circuits are established findings. Patients with SCZ have impaired verbal communication with a speech difficult to follow composed by unusual content and thought associations and have a deficit in the ability to discriminate facially expressed emotions. Some studies describes that SCZ patients had reduced GM volume and also decreased surface area in left fusiform gyrus, when compared to BPD patients, suggesting a disturbance in neural functions, affecting the ability to recognize facial emotions and their intensities. (14,46,51) However, other studies suggest a lower GM concentration in bilateral inferior temporal gyrus merging with fusiform gyrus and the gyrus rectus, either in first episode or chronic SCZ and not only in left fusiform gyrus. (47,48) GM volume in BPD patients is higher than the volume in SCZ patients in bilateral fusiform gyrus. (7) Furthermore, thickness or volume reduction in fusiform cortex is associated with increased vulnerability to affective disorders like BPD, especially in left

fusiform gyrus, but in our results, no differences, when comparing with SCZ patients, were found in left hemisphere volume in the BPD group, probably because some studies also referred a similar pattern of cortical thinning in SCZ patients. (11,14,15,52,53) Patients with higher decreases of GM in inferior temporal and fusiform gyrus present severe delusional symptoms, auditory verbal hallucinations, suspiciousness, and anxiety and also suggest an inverse correlation between GM volume and illness duration. (46–48) Through time, only SCZ patients show ongoing GM reduction in fusiform gyrus when compared to schizotypal disorders like BPD type 1, a fact that is not verified in a milder form of SCZ spectrum disorder. (48) In addition, GM in anterior fusiform gyrus was found to be smaller in SCZ patients, while posterior fusiform gyrus had smaller GM volumes in both SCZ patients and schizotypal disorder patients, which suggests that anterior fusiform gyrus modifications and an active pathological process are necessary to develop full-blown SCZ. (48,49) Although the division between anterior and posterior parts of the fusiform gyrus, total fusiform gyrus GM is reduced in SCZ, but not in schizotypal disorder, in accordance with our results. (49) BPD group had right-sided intrinsic connectivity distribution in fusiform gyrus with limbic, prefrontal regions and cerebellum. Furthermore, previous studies also refer low local gyrification index in the right fusiform gyrus in BPD patients and decreased functional connectivity to sensorimotor area and right superior temporal gyrus. (50,53) Although our results are mainly in line with previous studies, some ambiguity is shown in hemispheres GM volumes between conditions.

Finally, a cluster corresponding to BA11, BA25 and BA32 in the medial frontal gyrus and ACC in the right hemisphere was also found to have higher AI in BPD patients than in SCZ patients, indicating that BPD patients had a stronger rightward asymmetry than SCZ patients. Comparing SCZ and BPD groups, BPD patients had higher GM volume in right hemisphere and SCZ patients had higher GM volume in left hemisphere. The medial frontal gyrus controls several cognitive processes, such as decision-making, motor planning and discrimination, that are compromised in SCZ. Orbitofrontal cortex (BA11) is part of prefrontal cortex and plays a role in affective and cognitive processes, such as working memory, attentional control, emotional processing, expectation of reward and punishment, decision-making ability, cognitive inhibition, impulse control and flexibility. (54–56) Orbitofrontal cortex has a medial subregion, straight gyrus, and a lateral subregion, orbital gyrus. The lateral subregion is involved in the valuation of decision options and is more sensitive to loss of reward, whereas medial subregion is more sensitive to the presence of rewards. (55) The straight gyrus is an extension of the ACC onto the frontal cortex. (19) The straight gyrus has also dense inhibitory connections with

the auditory cortex and the superior temporal gyrus. Changes in laterality of the straight gyrus reveal dysfunction of these connections and might play a significant role in hallucinations and self-disorder symptoms in SCZ. A study shows bilateral GM reduction of the orbital gyrus, but not of the straight gyrus in SCZ patients. (55) On the other hand, BPD patients, exhibit GM reductions in both subregions of orbitofrontal cortex. (56) Global GM volume in orbitofrontal cortex is reduced in SCZ and BPD patients and is associated with poor executive functions. Executive function is related to the fronto-cingulo-parietal circuit, so dysregulation of this area may play an important role in pathophysiology of SCZ and BPD. In addition, decreased GM volume in orbitofrontal cortex is correlated with positive symptoms in SCZ and deficient emotional processes. (54,55) Furthermore, another study not only correlated GM volume decrease with positive symptoms, but also with negative symptoms, so it is not clear which specific symptoms are related to orbitofrontal cortex. (19) Moreover, the ACC (including BA25 and BA32) is part of brain's limbic system and a component of the prefrontal cortex. It is responsible for modulating prefrontal and limbic processes, especially in evaluating negative stimuli, attention, acquiring and using social information to guide decisions and cognitive processes such as inferring others' emotions. (57) The ACC is divided into two subregions, a dorsal cognitive subregion which is part of a distributed attentional network, which is described to had GM volume reduction in SCZ and BPD, (11,13,19,54) and a ventral cognitive affective subregion, primarily involved in regulate emotional and motivational information and response. (19) GM volume reduction is found with more consistency in SCZ patients and has direct relation to duration of illness. (13,19,58) In accordance with our results, two other studies showed that decreased GM volume was found in left ACC in patients with BPD and that there was higher GM volume in right ACC in BPD patients when compared to SCZ group. (7,59) Bilateral ACC has a difference in volume between patients with BPD and SCZ. In addition to cortical volume reduction, SCZ patients also exhibited reduced cortical thickness in ACC when compared to BPD patients. (14) ACC has connections with prefrontal, striatal and limbic regions, including orbitofrontal cortex, so a disruption in these networks compromises affective regulation and cognition and this mechanism is described for BPD. (13) In addition, reductions in WM were also found in right ACC for SCZ patients. (12) GM reduction and hypoactivation of ACC during emotional processing tasks in patients with psychosis is related to negative symptoms. The greater the negative symptoms like avolition and anhedonia, the greater the decrease of ACC activation to pleasant stimuli in SCZ. (9,19,57) However, anxiety is associated with prefrontal cortex hyperactivation. (9) This fact could be explained because anxiety and avolition are opposite endings of a continuum; anxiety is an extreme worry for the future, whereas avolition indicates a lack of interest in the

future. Avolition has a strong relationship with GM asymmetry. (9) Negative symptoms have a strong association with ACC and scales scores of emotional withdrawal and difficulty in abstract thinking. On the other hand, scale scores of stereotyped thinking are more related to the straight gyrus in orbitofrontal cortex. (19) Prefrontal GM reduction negatively correlates with impulsivity in BPD patients. (56) Despite some unknown facts in literature, structural evidences found by us are as described by other studies, although the exact functions of these areas are yet to discover.

Despite our study's rigorous design, matching for relevant variables such as gender and age and namely inclusion/exclusion criteria, some limitations should be discussed. The relatively small sample size, namely of particular small subgroups such as non-psychotic BPD patients, precludes the assessment of some variables, e.g. the influence of psychotic symptoms in BPD. While we assessed and controlled for current medication use, namely antipsychotics and lithium, its possible effect as a confounder cannot be entirely ruled out.

Although our structural findings match with recent studies, future research on this subject is necessary to not only better understand and validate the potential biomarkers described, to ensure the findings reported here can be translated to clinical practice, but also to understand which areas are responsible for each symptom that differentiate SCZ and BPD. To our knowledge, there is not only one area responsible for one specific symptom but is the disruption of the connections between those areas together with structural deficits, like GM volume asymmetry, that causes different expressions of the diseases.

To conclude, in this grey matter asymmetry study, we found brain areas with statistically different asymmetry index between schizophrenia and bipolar disorder patients. Namely, we found an asymmetry index higher in bipolar disorder patients when compared to schizophrenia patients in Brodmann areas 6, 11 and 37 and anterior cingulate cortex and an asymmetry index higher in schizophrenia patients when compared to bipolar disorder patients in the cerebellum. These promising results can be, in the future, translated to clinical practice to help clinicians in the challenging task of differential diagnosis.

REFERENCES

1. Jauhar S, Johnstone M, McKenna PJ. Schizophrenia. The Lancet [Internet]. 2022 Jan 29;399(10323):473–86. Available from: https://linkinghub.elsevier.com/retrieve/pii/S014067362101730X

2. Yeganeh-Doost P, Gruber O, Falkai P, Schmitt A. The role of the cerebellum in schizophrenia: From cognition to molecular pathways. Clinics. 2011;66(SUPPL.1):71–7.

3. Vieta E, Berk M, Schulze TG, Carvalho AF, Suppes T, Calabrese JR, et al. Bipolar disorders. Nat Rev Dis Primers [Internet]. 2018 Mar 8;4(1):18008. Available from: https://www.nature.com/articles/nrdp20188

4. Madeira N, Duarte JV, Martins R, Costa GN, Macedo A, Castelo-Branco M. Morphometry and gyrification in bipolar disorder and schizophrenia: A comparative MRI study. Neuroimage Clin. 2020 Jan 1;26:102220.

5. Lee DK, Lee H, Park K, Joh E, Kim CE, Ryu S. Common gray and white matter abnormalities in schizophrenia and bipolar disorder. PLoS One. 2020 May 1;15(5).

6. Eken A, Akaslan DS, Baskak B, Münir K. Diagnostic classification of schizophrenia and bipolar disorder by using dynamic functional connectivity: An fNIRS study. J Neurosci Methods. 2022 Jul 1;376.

7. Nenadic I, Maitra R, Langbein K, Dietzek M, Lorenz C, Smesny S, et al. Brain structure in schizophrenia vs. psychotic bipolar I disorder: A VBM study. Schizophr Res. 2015 Jul 1;165(2–3):212–9.

8. Sha Z, Schijven D, Francks C. Patterns of brain asymmetry associated with polygenic risks for autism and schizophrenia implicate language and executive functions but not brain masculinization. Mol Psychiatry. 2021 Dec 1;26(12):7652–60.

9. Núñez C, Paipa N, Senior C, Coromina M, Siddi S, Ochoa S, et al. Global brain asymmetry is increased in schizophrenia and related to avolition. Acta Psychiatr Scand. 2017 May 1;135(5):448–59.

10. Okada N, Fukunaga M, Yamashita F, Koshiyama D, Yamamori H, Ohi K, et al. Abnormal asymmetries in subcortical brain volume in schizophrenia. Mol Psychiatry. 2016 Oct 1;21(10):1460–6.

11. Dobri ML, Diaz AP, Selvaraj S, Quevedo J, Walss-Bass C, Soares JC, et al. The Limits between Schizophrenia and Bipolar Disorder: What Do Magnetic Resonance Findings Tell Us? Vol. 12, Behavioral Sciences. MDPI; 2022.

12. Sun Y, Chen Y, Collinson SL, Bezerianos A, Sim K. Reduced hemispheric asymmetry of brain anatomical networks is linked to schizophrenia: A connectome study. Cerebral Cortex. 2017;27(1):602–15.

13. Ellison-Wright I, Bullmore E. Anatomy of bipolar disorder and schizophrenia: A meta-analysis. Schizophr Res [Internet]. 2010;117(1):1–12. Available from: http://dx.doi.org/10.1016/j.schres.2009.12.022

14. Madre M, Canales-Rodríguez EJ, Fuentes-Claramonte P, Alonso-Lana S, Salgado-Pineda P, Guerrero-Pedraza A, et al. Structural abnormality in schizophrenia versus bipolar disorder: A whole brain cortical thickness, surface area, volume and gyrification analyses. Neuroimage Clin. 2020 Jan 1;25:102131.

15. Hibar DP, Westlye LT, Doan NT, Jahanshad N, Cheung JW, Ching CRK, et al. Cortical abnormalities in bipolar disorder: An MRI analysis of 6503 individuals from the ENIGMA Bipolar Disorder Working Group. Mol Psychiatry. 2018 Apr 1;23(4):932–42.

16. Wang Y, Wang J, Su W, Hu H, Xia M, Zhang T, et al. Symptom-circuit mappings of the schizophrenia connectome. Psychiatry Res [Internet]. 2023 May;323:115122. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0165178123000756

17. Andreasen NC, Pierson R. The Role of the Cerebellum in Schizophrenia. Biol Psychiatry [Internet]. 2008 Jul 15;64(2):81–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0006322308000498

18. Qi Z, Wang J, Gong J, Su T, Fu S, Huang L, et al. Common and specific patterns of functional and structural brain alterations in schizophrenia and bipolar disorder: a multimodal voxel-based meta-analysis. Journal of Psychiatry and Neuroscience [Internet]. 2022 Feb 1;47(1):E32–47. Available from: http://www.jpn.ca/lookup/doi/10.1503/jpn.210111

19. Kim GW, Kim YH, Jeong GW. Whole brain volume changes and its correlation with clinical symptom severity in patients with schizophrenia: A DARTEL-based VBM study. Hashimoto K, editor. PLoS One [Internet]. 2017 May

17;12(5):e0177251. Available from: https://dx.plos.org/10.1371/journal.pone.0177251

20. Espírito-Santo H, Pires CF, Garcia IQ, Daniel F, Silva AG da, Fazio RL. Preliminary validation of the Portuguese Edinburgh Handedness Inventory in an adult sample. Appl Neuropsychol Adult [Internet]. 2017;24(3):275–87. Available from: https://doi.org/10.1080/23279095.2017.1290636

21. Keshavan MS, Morris DW, Sweeney JA, Pearlson G, Thaker G, Seidman LJ, et al. A dimensional approach to the psychosis spectrum between bipolar disorder and schizophrenia: The Schizo-Bipolar Scale. Schizophr Res [Internet]. 2011 Dec [cited 2019 Aug 11];133(1–3):250–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21996268

22. McEvoy JP, Apperson LJ, Appelbaum PS, Ortlip P, Brecosky J, Hammill K, et al. Insight in schizophrenia. Its relationship to acute psychopathology. J Nerv Ment Dis. 1989/01/01. 1989;177(1):43–7.

23. Brissos S, Palhava F, Marques JG, Mexia S, Carmo AL, Carvalho M, et al. The Portuguese version of the Personal and Social Performance Scale (PSP): reliability, validity, and relationship with cognitive measures in hospitalized and community schizophrenia patients. Soc Psychiatry Psychiatr Epidemiol [Internet]. 2012;47(7):1077–86. Available from: https://www.ncbi.nlm.nih.gov/pubmed/21739224

24. Lukoff D, Liberman RP, Nuechterlein KH. Symptom Monitoring in the Rehabilitation of Schizophrenic Patients. Schizophr Bull. 1986;12(4):578–603.

25. Atkins M, Burgess A, Bottomley C, Riccio M. Chlorpromazine equivalents: a consensus of opinion for both clinical and research applications. Psychiatric Bulletin. 1997;21(4):224–6.

26. Kurth F, Gaser C, Luders E. A 12-step user guide for analyzing voxel-wise gray matter asymmetries in statistical parametric mapping (SPM). Nat Protoc [Internet]. 2015 Feb 15;10(2):293–304. Available from: http://www.nature.com/articles/nprot.2015.014

27. Luders E, Gaser C, Jancke L, Schlaug G. A voxel-based approach to gray matter asymmetries. Neuroimage. 2004 Jun 1;22(2):656–64.

28. Klein A, Andersson J, Ardekani BA, Ashburner J, Avants B, Chiang MC, et al. Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. Neuroimage. 2009 Jul 1;46(3):786–802.

29. Ashburner J, Friston KJ. Why Voxel-Based Morphometry Should Be Used. Neuroimage. 2001 Dec 1;14(6):1238–43.

30. Chrobak AA, Siuda-Krzywicka K, Siwek GP, Tereszko A, Janeczko W, Starowicz-Filip A, et al. Disrupted implicit motor sequence learning in schizophrenia and bipolar disorder revealed with ambidextrous Serial Reaction Time Task. Prog Neuropsychopharmacol Biol Psychiatry. 2017 Oct 3;79:169–75.

31. Picard H, Amado I, Mouchet-Mages S, Olié JP, Krebs MO. The role of the cerebellum in schizophrenia: An update of clinical, cognitive, and functional evidences. Vol. 34, Schizophrenia Bulletin. 2008. p. 155–72.

32. Duarte JV, Abreu R, Castelo-Branco M. A two-stage framework for neural processing of biological motion. Neuroimage. 2022 Oct 1;259:119403.

33. Duarte JV, Costa GN, Martins R, Castelo-Branco M. Pivotal role of hMT+ in long-range disambiguation of interhemispheric bistable surface motion. Hum Brain Mapp. 2017 Oct 1;38(10):4882–97.

34. Duarte JV, Faustino R, Lobo M, Cunha G, Nunes C, Ferreira C, et al. Parametric fMRI of paced motor responses uncovers novel whole-brain imaging biomarkers in spinocerebellar ataxia type 3. Hum Brain Mapp. 2016 Oct 1;37(10):3656–68.

35. Chrobak AA, Siuda-Krzywicka K, Sołtys Z, Siwek GP, Bohaterewicz B, Sobczak AM, et al. Relationship between neurological and cerebellar soft signs, and implicit motor learning in schizophrenia and bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry [Internet]. 2021 Dec 20 [cited 2023 Mar 7];111:110137. Available from: https://linkinghub.elsevier.com/retrieve/pii/S027858462030453X

36. Venkatasubramanian G, Jayakumar PN, Gangadhar BN, Keshavan MS. Neuroanatomical correlates of neurological soft signs in antipsychotic-naive schizophrenia. Psychiatry Res Neuroimaging. 2008 Dec 30;164(3):215–22.

37. Lei W, Kirkpatrick B, Wang Q, Deng W, Li M, Guo W, et al. Progressive brain structural changes after the first year of treatment in first-episode treatment-naive patients with deficit or nondeficit schizophrenia. Psychiatry Res Neuroimaging. 2019 Jun 30;288:12–20.

38. Stein J. Sensorimotor control. In: The Curated Reference Collection in Neuroscience and Biobehavioral Psychology. Elsevier Science Ltd.; 2016.

39. Hirjak D, Meyer-Lindenberg A, Fritze S, Sambataro F, Kubera KM, Wolf RC. Motor dysfunction as research domain across bipolar, obsessive-compulsive and neurodevelopmental disorders. Neurosci Biobehav Rev. 2018 Dec 1;95:315–35.

40. Intaitė M, Duarte JV, Castelo-Branco M. Working memory load influences perceptual ambiguity by competing for fronto-parietal attentional resources. Brain Res. 2016 Nov 1;1650:142–51.

41. Molina V, Galindo G, Cortés B, Hernández JA. Voxel-Based Morphometry Comparison Between Chronic Schizophrenia And Bipolar Patients And Healthy Controls. Schizophr Res [Internet]. 2010 Apr 1 [cited 2023 Mar 7];117(2–3):341. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0920996410006778

42. Caligiuri MP, Brown GG, Meloy MJ, Eyler LT, Kindermann SS, Eberson S, et al. A functional magnetic resonance imaging study of cortical asymmetry in bipolar disorder. 2004.

43. Exner C, Weniger G, Schmidt-Samoa C, Irle E. Reduced size of the pre-supplementary motor cortex and impaired motor sequence learning in first-episode schizophrenia. Schizophr Res. 2006 Jun;84(2–3):386–96.

44. Cotovio G, Rodrigues da Silva D, Real Lage E, Seybert C, Oliveira-Maia AJ. Hemispheric asymmetry of motor cortex excitability in mood disorders – Evidence from a systematic review and meta-analysis. Clinical Neurophysiology. 2022 May 1;137:25–37.

45. Hui Y, Qing Q, Jize J, Hui X, Zhenggui Y, Yu Z, et al. Explore functional brain changes in bipolar disorder: A whole brain ale meta-analysis. Rev Psiquiatr Clín. 2021;48(4):208–15.

46. Jung S, Lee A, Bang M, Lee SH. Gray matter abnormalities in language processing areas and their associations with verbal ability and positive symptoms in first-episode patients with schizophrenia spectrum psychosis. Neuroimage Clin. 2019 Jan 1;24.

47. Mennigen E, Jiang W, Calhoun VD, van Erp TGM, Agartz I, Ford JM, et al. Positive and general psychopathology associated with specific gray matter reductions in inferior temporal regions in patients with schizophrenia. Schizophr Res. 2019 Jun 1;208:242–9.

48. Takahashi T, Zhou SY, Nakamura K, Tanino R, Furuichi A, Kido M, et al. A follow-up MRI study of the fusiform gyrus and middle and inferior temporal gyri in schizophrenia spectrum. Prog Neuropsychopharmacol Biol Psychiatry. 2011 Dec 1;35(8):1957–64.

49. Takahashi T, Suzuki M, Zhou SY, Tanino R, Hagino H, Niu L, et al. Temporal lobe gray matter in schizophrenia spectrum: A volumetric MRI study of the fusiform gyrus, parahippocampal gyrus, and middle and inferior temporal gyri. Schizophr Res. 2006 Oct;87(1–3):116–26.

50. Goldman DA, Sankar A, Rich A, Kim JA, Pittman B, Constable RT, et al. A graph theory neuroimaging approach to distinguish the depression of bipolar disorder from major depressive disorder in adolescents and young adults. J Affect Disord. 2022 Dec 15;319:15–26.

51. Jung S, Kim JH, Kang NO, Sung G, Ko YG, Bang M, et al. Fusiform gyrus volume reduction associated with impaired facial expressed emotion recognition and emotional intensity recognition in patients with schizophrenia spectrum psychosis. Psychiatry Res Neuroimaging. 2021 Jan 30;307.

52. Chen MH, Kao ZK, Chang WC, Tu PC, Hsu JW, Huang KL, et al. Increased Proinflammatory Cytokines, Executive Dysfunction, and Reduced Gray Matter Volumes In First-Episode Bipolar Disorder and Major Depressive Disorder. J Affect Disord. 2020 Sep 1;274:825–31.

53. Chen C, Liu Z, Zuo J, Xi C, Long Y, Li MD, et al. Decreased Cortical Folding of the Fusiform Gyrus and Its Hypoconnectivity with Sensorimotor Areas in Major Depressive Disorder. J Affect Disord. 2021 Dec 1;295:657–64.

54. Yang Y, Li X, Cui Y, Liu K, Qu H, Lu Y, et al. Reduced Gray Matter Volume in Orbitofrontal Cortex Across Schizophrenia, Major Depressive Disorder, and Bipolar Disorder: A Comparative Imaging Study. Front Neurosci. 2022 Jun 10;16.

55. Takayanagi Y, Takahashi T, Orikabe L, Masuda N, Mozue Y, Nakamura K, et al. Volume reduction and altered sulco-gyral pattern of the orbitofrontal cortex in first-episode schizophrenia. Schizophr Res [Internet]. 2010 Aug;121(1–3):55–65. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0920996410013022

56. Carroll AL, Damme KSF, Alloy LB, Bart CP, Ng TH, Titone MK, et al. Risk for bipolar spectrum disorders associated with positive urgency and orbitofrontal

cortical grey matter volume. Neuroimage Clin [Internet]. 2022 Jan 1;36:103225. Available from: https://linkinghub.elsevier.com/retrieve/pii/S221315822200290X

57. Nelson BD, Bjorkquist OA, Olsen EK, Herbener ES. Schizophrenia symptom and functional correlates of anterior cingulate cortex activation to emotion stimuli: An fMRI investigation. Psychiatry Res Neuroimaging. 2015 Dec 30;234(3):285–91.

58. Frascarelli M, Tognin S, Mirigliani A, Parente F, Buzzanca A, Torti MC, et al. Medial frontal gyrus alterations in schizophrenia: Relationship with duration of illness and executive dysfunction. Psychiatry Res Neuroimaging. 2015 Feb 28;231(2):103–10.

59. Wang X, Luo Q, Tian F, Cheng B, Qiu L, Wang S, et al. Brain grey-matter volume alteration in adult patients with bipolar disorder under different conditions: A voxel-based meta-analysis. Journal of Psychiatry and Neuroscience. 2019 Mar 1;44(2):89–101.