



Morphometry and gyrification in bipolar disorder and schizophrenia: A comparative MRI study

Nuno Madeira^{a,d,e,1}, João Valente Duarte^{a,d,e,1}, Ricardo Martins^{a,d,e},
Gabriel Nascimento Costa^{a,d,e}, António Macedo^{a,b,c}, Miguel Castelo-Branco^{a,d,e,*}

^a Coimbra Institute for Biomedical Imaging and Translational Research (CIBIT), University of Coimbra, Portugal

^b Institute of Psychological Medicine, Faculty of Medicine, University of Coimbra, Portugal

^c Department of Psychiatry, Centro Hospitalar e Universitário de Coimbra, Portugal

^d Institute of Nuclear Sciences Applied to Health (ICNAS), University of Coimbra, Portugal

^e Institute for Biomedical Imaging and Life Sciences (CNC.IBILI), Faculty of Medicine, University of Coimbra, Portugal

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ABSTRACT

Schizophrenia is believed to be a neurodevelopmental disease with high heritability. Differential diagnosis is often challenging, especially in early phases, namely with other psychotic disorders or even mood disorders, such as bipolar disorder with psychotic symptoms. Key pathophysiological changes separating these two classical psychoses remain poorly understood, and current evidence favors a more dimensional than categorical differentiation between schizophrenia and bipolar disorder. While established biomarkers like cortical thickness and grey matter volume are heavily influenced by post-onset changes and thus provide limited possibility of accessing early pathologies, gyrification is assumed to be more specifically determined by genetic and early developmental factors. The aim of our study was to compare both classical and novel morphometric features in these two archetypal psychiatric disorders. We included 20 schizophrenia patients, 20 bipolar disorder patients and 20 age- and gender-matched healthy controls. Data analyses were performed with CAT12/SPM12 applying general linear models for four morphometric measures: gyrification and cortical thickness (surface-based morphometry), and whole-brain grey matter/grey matter volume (voxel-based morphometry - VBM). Group effects were tested using age and gender as covariates (and total intracranial volume for VBM). Voxel-based morphometry analysis revealed a schizophrenia vs. control group effect on regional grey matter volume ($p < 0.05$, familywise error correction) in the right globus pallidus. There was no group effect on white matter volume when correcting for multiple comparisons neither on cortical thickness. Gyrification changes in clinical samples were found in the left supramarginal gyrus (BA40) – increased and reduced gyrification, respectively, in BPD and SCZ patients – and in the right inferior frontal gyrus (BA47), with a reduction in gyrification of the SCZ group when compared with controls. The joint analysis of different morphometric features, namely measures such as gyrification, provides a promising strategy for the elucidation of distinct phenotypes in psychiatric disorders. Different morphological change patterns, highlighting specific disease trajectories, could potentially generate neuroimaging-derived biomarkers, helping to discriminate schizophrenia from bipolar disorder in early phases, such as first-episode psychosis patients.

1. Introduction

The classical dichotomy between schizophrenia (SCZ) and bipolar disorder (BPD) proposed by Kraepelin has dominated western psychiatry for over a century, and only recently has a distinction that could be more dimensional than categorical emerged (Craddock et al., 2009).

Several studies have documented a high genetic overlap between SCZ and BPD (Cross-Disorder Group of the Psychiatric Genomics, 2013; Hammerschlag et al., 2019). Clinically, early phases of SCZ and BPD can be hard to differentiate due to common presentations, especially when psychotic symptoms are prominent in BPD. In the AESOP-10 study, around 30% of patients who had a first-episode psychosis were

* 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: mcbranco@fmed.uc.pt (M. Castelo-Branco).

¹ Both authors contributed equally to this work.

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later diagnosed with an affective psychosis (BPD or unipolar depression) over a 10-year follow-up (Morgan et al., 2014). Identification of diagnosis-specific biomarkers that can help to differentiate SCZ and BPD has been the subject of intensive investigation, not least because the treatment options are substantially different and might impact morbidity and mortality.

Structural brain changes are good candidates for exploration as biological markers in both conditions (Lewis and Levitt, 2002; Rapoport et al., 2012). A seminal computerized tomography (CT) study documented increased ventricular volume in patients with SCZ compared to age-matched controls (Johnstone et al., 1976), and ventricular enlargement and deep regional grey matter volumes measured using voxel-based morphometry are to date the most consistent and replicated neuroimaging findings in SCZ (Brugger and Howes, 2017; Glahn et al., 2008).

A comparative meta-analysis of voxel-based morphometry studies has shown extensive grey matter (GM) loss in frontotemporal, cingulate and insular cortices, and increased GM in basal ganglia in SCZ, while in BPD grey matter reductions were present in the anterior cingulate cortex and the insula (Ellison-Wright and Bullmore, 2010). Recently, a direct comparison of SCZ vs. BPD suggested that more extensive prefrontal, thalamic, and hippocampal deficits might set apart schizophrenia, although authors could not exclude effects of clinical heterogeneity, especially in BPD patients, namely comorbid psychotic symptoms (Nenadic et al., 2015b). Gender differences in GM volumes are a known source of heterogeneity in comparisons between SCZ and BPD; when gender is controlled for, GM abnormalities are mostly restricted to fronto-insular cortex in BPD and dorsolateral prefrontal cortex in SCZ, while GM reduction of the anterior cingulate cortex is seen in both populations (Bora et al., 2012). Disease stage/chronicity of disease (Chan et al., 2011; Shah et al., 2016) and antipsychotic treatment (Torres et al., 2013) are additional sources of variability in VBM analyses.

Surface-based morphometry techniques enable the analysis of additional brain features including surface area, curvature, cortical thickness (Fischl and Dale, 2000) and cortical gyrification (Schaefer et al., 2008). Cortical thickness has been shown to be reduced in schizophrenia in prefrontal and temporal cortical areas (Besteher et al., 2016; Goldman et al., 2009; Kubota et al., 2011; Nesvåg et al., 2008), but the effects are also modulated by illness duration and antipsychotic treatment (van Haren et al., 2011). Cortical structural changes in BPD patients are less prominent except in patients with comorbid psychosis (Godwin et al., 2018; Hibar et al., 2018; Rimol et al., 2012).

Cortical gyrification of the brain represents the characteristic folding of the cerebral cortex. It has been hypothesized that alternative neuroimaging biomarkers might be more disease-specific and could help disentangle shared findings in both SCZ and BPD, and potentially overperform classical markers such as cortical thickness and GM volume, which may be more influenced by post-onset pathological processes (Nenadic et al., 2015a). Cortical gyrification has been proposed as a novel schizophrenia endophenotype candidate, since it targets morphometric properties which are not captured by VBM or cortical thickness analyses, and is assumed to be more specifically determined by genetic and developmental factors (Nenadic et al., 2015a; Zilles et al., 2013, 1988). Accordingly, we have recently shown that a monogenetically determined neurodevelopmental disorder, Neurofibromatosis Type 1 is characterized by abnormal gyrification which is consistent with patterns of cognitive dysfunction observed in this condition (Violante et al., 2013). This feature has also been explored in schizophrenia, modelled as a late neurodevelopmental disorder with high heritability (Matsuda and Ohi, 2018; Spalthoff et al., 2018). While abnormal cortical gyrification has been reported in patients with SCZ, patient relatives and at-risk individuals, conflicting findings of hyper- and hypo-gyrification have been reported which may be explained by different estimation methods and other factors such as age, gender and illness stage and severity (Matsuda and Ohi, 2018). Cortical gyrification

can be quantified as a gyrification index (GI), which in SCZ and BPD has been shown to decrease at a faster pace than in healthy controls during aging, especially after the age of 40 (Bo Cao et al., 2017). Evidence regarding gyrification changes in BPD is more scarce, but studies have shown reduced prefrontal gyrification and a significant disease-stage effect on the GI of patients with BPD (B. Cao et al., 2017; McIntosh et al., 2009).

An important caveat of case-control studies, which dominate the field of neuroimaging in psychiatry, is that patients are enrolled based on a specific clinical diagnosis and are compared with healthy individuals, but typically not to another clinical group (Etkin, 2019). Taking into account other previous limitations in studying brain structural differences between SCZ and BPD, our main purpose was to directly compare carefully defined matched-groups of bipolar disorder (BPD) vs. schizophrenia (SCZ) patients and healthy controls using both conventional (GM volume and cortical thickness) and novel (gyrification index) morphometric features of these archetypal psychiatric disorders. We hypothesize that analyzing well-matched disease populations will allow the isolation of disease-specific morphometric markers which may inform and guide future research.

2. Methods

2.1. Participants

We included outpatients with schizophrenia (SCZ) and bipolar disorder (BPD) from a major university hospital, besides healthy controls (CNT), matched for age, gender and education. Inclusion criteria for clinical groups were: (1) ICD-10 criteria for SCZ or BPD using a semi-structured interview (Martins et al., 2019); (2) age between 18–54; (3) capacity to consent; (4) right-handedness through evaluation with the Edinburgh Handedness Inventory (Espírito-Santo et al., 2017); (5) clinical stability in the last 12 weeks prior to enrollment. General exclusion criteria were: (1) medical or neurological comorbidity (e.g. epilepsy, head trauma, neurodevelopmental disorders); (2) substance abuse/dependence; (3) contra-indications to magnetic resonance imaging. Patients' clinical assessment included instruments such as the Brief Psychiatric Rating Scale – BPRS (Lukoff et al., 1986) for general psychopathology, and the Personal and Social Performance Scale – PSP (Brissos et al., 2012) addressing functioning; insight was measured through the Insight and Treatment Attitudes Questionnaire, ITAQ (McEvoy et al., 1989). The Schizo-Bipolar Scale (Keshavan et al., 2011), developed to capture the dimensional interaction between psychosis and affective symptoms, was also administered. Current antipsychotic exposure in patient groups (SCZ and BPD) was calculated through chlorpromazine equivalents – CPZE (Atkins et al., 1997). Control individuals were recruited from the institution's workers and their relatives, and a brief interview excluded a personal or family history of mental disorders, namely SCZ or BPD, in addition to general exclusion criteria. All participants provided written informed consent to a study approved by the local Ethics Committee of the Faculty of Medicine of the University of Coimbra (ref. CE-010/2014) and in accordance with the Declaration of Helsinki.

2.2. Magnetic resonance imaging (MRI) acquisition

Data were collected with a Siemens Magnetom TIM Trio 3 Tesla scanner (Siemens, Munich, Germany) with a phased array 12-channel birdcage head coil. We acquired a 3D anatomical T1-weighted MPRAGE (magnetization-prepared rapid gradient echo) magnetic resonance imaging pulse sequence (TR 2530 ms; TE 3.42 ms; TI = 1100 ms; flip angle 7°; 176 single-shot interleaved slices with no gap with isotropic voxel size 1 × 1 × 1 mm; FOV 256 mm) of all 60 participants.

2.3. Pre-processing

All images were processed and analyzed using the CAT12 toolbox (C. Gaser, Structural Brain Mapping Group, Jena University Hospital, Jena, Germany; <http://dbm.neuro.uni-jena.de/cat/>) implemented in SPM12 (Wellcome Trust center for Neuroimaging, London, UK; <http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). CAT12 served as the platform for all the analyses, as it offers processing pipelines for both voxel-based morphometry as well as surface-based morphometry (including cortical thickness and gyrification), allowing us to perform all analyses with this software package. For processing- and analysis-steps, pre-set parameters in accordance with standard protocol (<http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf>) were used, applying default settings unless indicated otherwise. This tool has been previously used and validated in morphometric studies in schizophrenia (Spalthoff et al., 2018), as well as in other neurologic and neurodegenerative diseases (Righart et al., 2017; Seiger et al., 2018). Processing also included a two-step quality assurance: first, all images were visually inspected for artefacts (prior to pre-processing); secondly, all underwent a statistical quality control for inter-subject homogeneity and overall image quality as included in the CAT12 toolbox (“check homogeneity” function) after segmentation. This second step again included a visual inspection procedure for potential newly introduced artefacts.

We used a volume-based tool (CAT12) which offers an alternative that allows for faster processing (1 h per subject) and rapid learning by the user while at the same time maintaining a high quality, when compared to the well-established surface-based tool FreeSurfer. FreeSurfer's steep learning curve for beginner users and high processing time might demand considerable computational and time effort, particularly in larger studies. On the one hand, spherical and brain phantoms have confirmed that CAT accurately measures features of cortical thickness and folding (Dahnke et al., 2013). On the other hand, CAT12 has been validated in clinical populations, and there is evidence that CAT12 can be considered a fast and reliable alternative to FreeSurfer (Righart et al., 2017; Seiger et al., 2018).

2.4. Gyrification analysis

We calculated local (vertex-wise) gyrification index (GI) maps based on the absolute mean curvature approach (Luders et al., 2006). Extraction of the cortical surface (using CAT12 routines) resulted in the construction of a mesh of the central surface, i.e. the surface between the grey matter/CSF border and the grey matter/white matter boundary (Dahnke et al., 2013). We then calculated the local absolute mean curvature of this central surface by averaging the mean curvature values from each vertex point within 3 mm from a given point. In a second step, we applied 15 mm full-width at half maximum (FWHM) smoothing to the GI maps. This method has been applied in previous studies, also with other processing pipelines for cortical surface extraction (Luders et al., 2012; Nenadic et al., 2015b).

2.5. Cortical thickness analysis

We analyzed cortical thickness based on the same algorithm for extraction of the cortical surface implemented in CAT12, as given above for GI analyses. Here, the central surface as well as cortical thickness are estimated in one step using a projection-based distance measure (Dahnke et al., 2013). The vertex-wise cortical thickness measures were resampled and smoothed using a 15 mm FWHM Gaussian kernel.

2.6. Voxel-based morphometry (VBM)

We applied spatial normalization and segmentation into three voxel classes: grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) using partial volume segmentation with adaptive maximum a

posteriori (MAP) approach. We also determined total intracranial volume (TIV) for all scans. Using modulated normalized GM maps, we tested the hypothesis of regional grey matter volume (GMV) differences. The extracted GM maps were smoothed using a 12 mm FWHM kernel and used for further analysis. We applied a 0.1 absolute masking threshold to the VBM data.

2.7. Statistical analysis

We performed statistical analyses of imaging data in the CAT12/SPM12 statistical module applying ANOVA to each of the three morphometric measures (gyrification and cortical thickness with SBM, and GM volume with VBM). Using age and gender as covariates (and for VBM analyses, additionally, total intracranial volume, TIV), we tested group differences applying thresholds of $p < 0.05$ with FWE correction for multiple comparisons. When the FWE was too stringent, and not to miss an exploratory interesting effect, we thresholded the statistical map at voxel level with $p < 0.001$ and then corrected at the cluster level with non-stationary cluster extent correction. In addition, when there was a significant group effect, we did post-hoc pairwise comparisons with t -test to detect differences between every pair of groups, using Bonferroni correction for multiple comparisons.

Demographic and clinical data analysis was performed with IBM SPSS Statistics 23 (IBM Corporation, New York, EUA). Normality of the data was tested using the Shapiro–Wilk test. When data were normally distributed, parametric ANOVA and t -tests were used to test differences between groups, and Pearson correlation was used to calculate correlation between imaging and clinical data. If the assumption of normality was not met, non-parametric Kruskal–Wallis H test and Mann–Whitney U tests were used to assess between-group differences, while Spearman correlation was used to assess the relationship between morphometric measures and clinical scores.

Study design and data analysis were aligned with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) consensus (Vandenbroucke et al., 2007).

3. Results

3.1. Descriptive analysis

Demographic and clinical data are summarized in Table 1. Regarding inpatient admissions of BPD participants, most (58%) were due to manic episodes; all admissions of patients with SCZ involved psychotic relapses. All patients with SCZ ($n = 20$) were on stable antipsychotic (AP) medication, predominantly atypical APs: one second-generation AP ($n = 16$), a combination of two second-generation AP ($n = 2$) or a first-generation AP ($n = 2$). In the BPD group ($n = 20$), two patients were stable without any medication; most individuals ($n = 18$) were on regular mood-stabilizing medication: mood-stabilizer monotherapy ($n = 7$), mood-stabilizers in association ($n = 1$), a mood-stabilizer and atypical AP combination ($n = 4$), and atypical AP, either in monotherapy ($n = 4$) or combination ($n = 2$). Only one individual was medicated with lithium.

Patient groups (SCZ and BPD) had no relevant demographic or clinical differences besides antipsychotic exposure, greater in SCZ patients ($p = 0.032$). Regarding psychopathological evaluation, patients with SCZ had greater ($p < 0.001$) general psychopathology scores, and worse ($p = 0.001$) functioning than BPD patients. Individuals in the BPD group had higher ($p = 0.044$) insight than SCZ patients. As expected, the SCZ group had much higher scores ($p < 0.001$) on the Schizo-Bipolar Scale than BPD individuals: higher scores are associated with prototypical SCZ syndromes, while paradigmatic BPD cases score lower (Keshavan et al., 2011).

Groups were balanced for gender, exactly the same within-group distribution ($\chi^2(2) = 0.000$, $p = 1.000$), and age. The data on estimated total intracranial volume (TIV) and total grey matter (GM) distribution

Table 1
Demographic and clinical data of study groups.

N=	Schizophrenia 20	Bipolar disorder 20	Healthy controls 20	test statistics	p-value
Gender distribution (female/male)	7/13	7/13	7/13	χ^2 0.000	1.000
Age - years (SD)	31.5 (10.3)	31.65 (10.0)	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
Total intracranial volume - ml (SD)	1469.31 (27.18)	1484.58 (37.73)	1523.80 (33.44)	F 0.710	.496
Age of disease onset - years (SD)	25.6 (6.9)	26.5 (8.8)	n/a	t -0.276	.784
Duration of disease - years (SD)	6.0 (7.9)	5.2 (4.3)	n/a	t 0.297	.769
Inpatient admissions (min-max)	1.25 (0–7)	1.25 (0–4)	n/a	t 0.000	1.000
Antipsychotic exposure (CPZE) – mg (SD)	380.0 (337.3)	160.8 (272.3)	n/a	t 2.226	.032
History of psychotic symptoms	20/20	16/20	n/a	χ^2 0.035	.106
History of substance abuse	5/20	7/20	n/a	χ^2 0.557	.731
History of suicidal behaviors	4/20	4/20	n/a	χ^2 0.000	1.000
Psychopathology - BPRS (SD)	35.65 (6.41)	29.11 (2.61)	n/a	t 3.991	.000
Functioning – PSP (SD)	80.22 (12.36)	92.00 (4.00)	n/a	t -3.845	.001
Insight – ITAQ (SD)	17.12 (3.16)	19.13 (2.22)	n/a	t -2.100	.044
Schizo-Bipolar Scale (min-max)	8.00 (7–9)	0.94 (0–2)	n/a	t 28.356	.000

BPRS = Brief Psychiatric Rating Scale; CPZE = chlorpromazine equivalents; ITAQ = Insight and Treatment Attitudes Questionnaire; PSP = Personal and Social Performance Scale; SD = standard deviation;

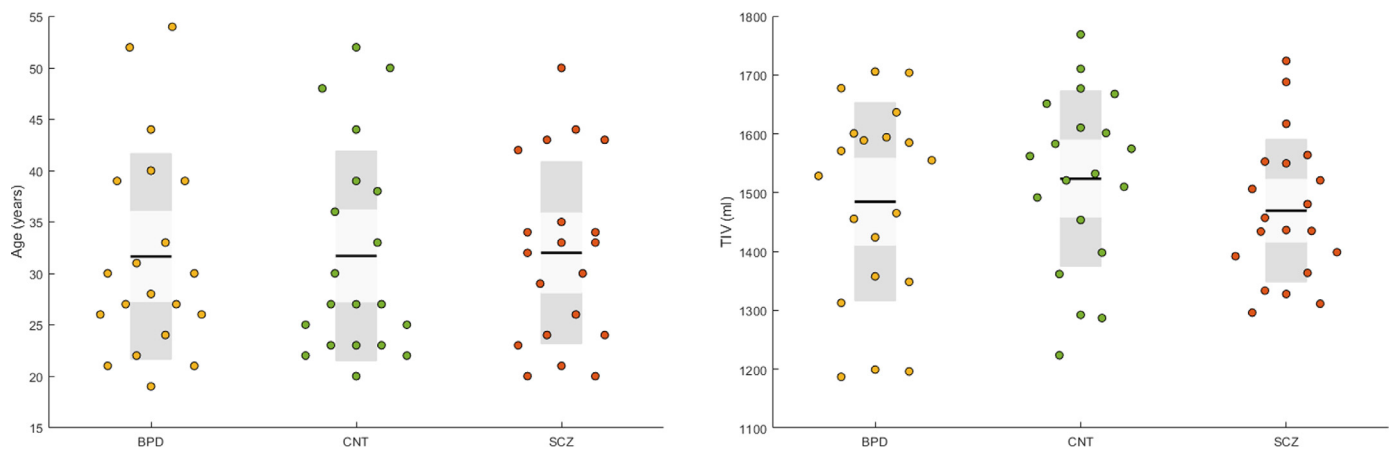


Fig. 1. Boxplots of the distribution of age (in years) and total intracranial volume (TIV, in ml) across participants in each group. No statistically significant differences were observed between groups.

were normally distributed for each group, as assessed by Shapiro–Wilk tests ($p > 0.05$ for all tests). There was no statistically significant difference in mean age between groups as determined by one-way ANOVA ($F(2,57) = 0.008$, $p = 0.992$). Adjusting the estimates of TIV and total GM for age, there was also no significant difference in mean TIV between groups ($F(2,57) = 0.710$, $p = 0.496$) or total GM volume ($F(2,57) = 1.471$, $p = 0.238$) between groups (Fig. 1).

3.2. Voxel-based morphometry

3.2.1. Grey matter volume

VBM analysis revealed a group effect on regional GM volume ($F = 23.99$; $p = 0.003$, FWE corrected) in the right globus pallidus, at MNI coordinates [18–2 5] (Fig. 2, top). Post-hoc analyses revealed significantly increased ($t = 6.62$; $p < 0.001$, with Bonferroni correction) GM volume in the right globus pallidus of SCZ patients compared to CNT (Fig. 2, bottom). We did not observe significant correlation between the volume of globus pallidus and age, TIV, total GM volume, disease duration or medication in any group (all $p > 0.05$).

3.3. Gyrfication analysis

Gyrfication analysis revealed a group effect on the gyrfication index in left supramarginal gyrus - BA40 ($F = 10.17$; $p < 0.001$) at MNI coordinates [–44 –45 41] and right inferior frontal gyrus - BA47

($F = 8.41$; $p = 0.001$) at MNI coordinates [32 40 –11]. Post-hoc analyses revealed increased gyrfication in patients with BPD compared to SCZ in the left supramarginal gyrus - BA40 ($t = 4.13$; $p < 0.001$, Bonferroni corrected), while local gyrfication index (LGI) of healthy controls was in between the clinical groups. SCZ patients had significantly decreased gyrfication compared to controls ($t = 3.37$; $p = 0.005$, Bonferroni corrected). In what regards the right inferior frontal gyrus - BA47, the SCZ group had lower gyrfication compared to healthy controls ($t = 4.18$; $p < 0.001$, Bonferroni corrected) and to BPD ($t = 2.52$; $p = 0.048$, Bonferroni corrected), which in turn had decreased gyrfication compared to controls as well, although not significantly. Results are shown in Fig. 3.

3.4. Correlational analysis between morphometric and psychopathological measures

We explored the relation between psychopathological data and right GP regional GM volume, namely in subgroups BPD, SCZ and controls. In BPD patients there was a negative association between GP volume and functioning – higher PSP score (Spearman rho = –0.503, $p = 0.024$), and also with insight – higher ITAQ score (Spearman rho = –0.462, $p = 0.040$). Similar correlations were found when analyzing both clinical samples as a single group: a larger GP volume was associated with worse functioning (Spearman rho = –0.359, $p = 0.023$) and insight (Spearman rho = –0.420, $p = 0.007$); a positive association

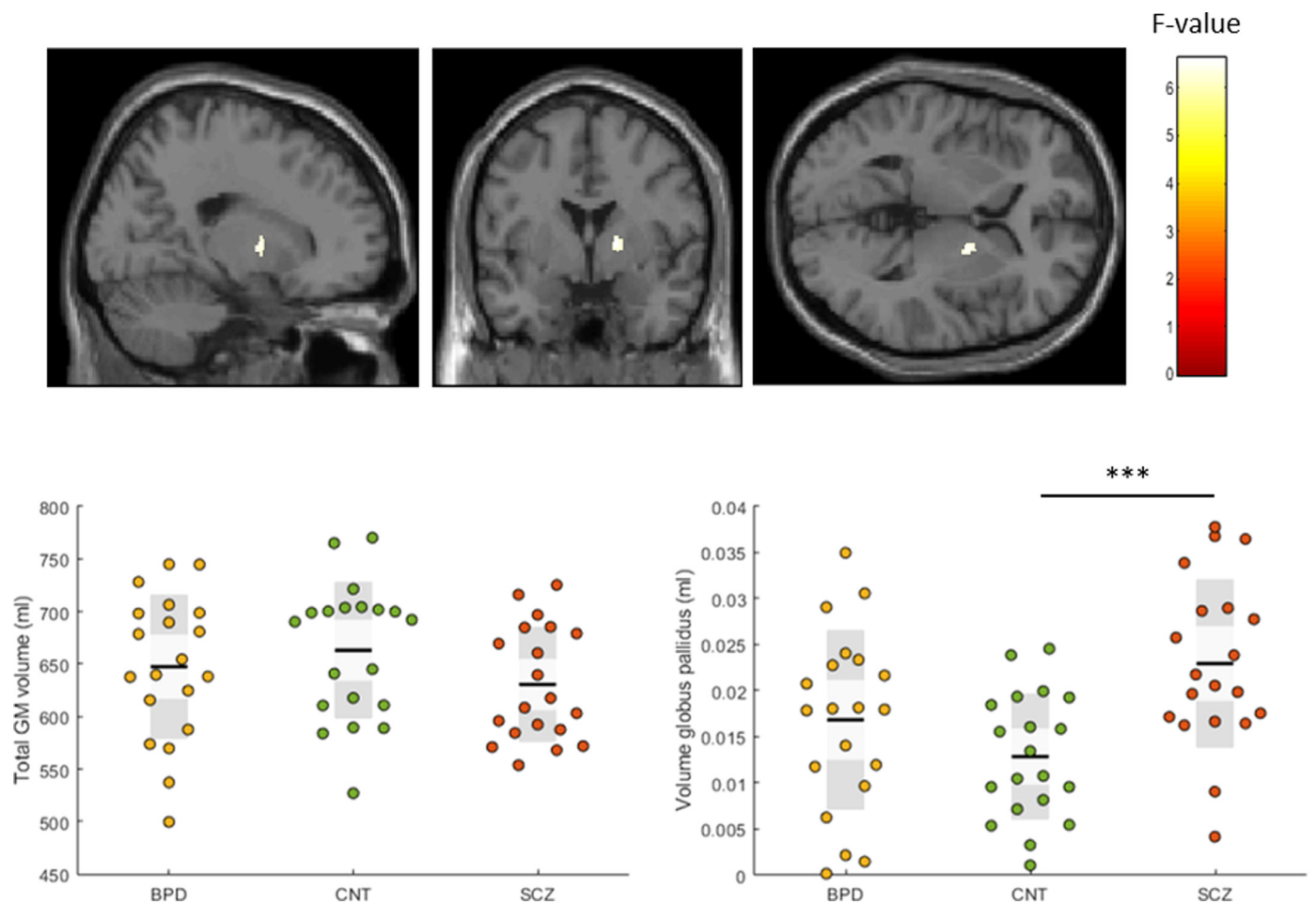


Fig. 2. *Top:* VBM analysis of group effects (schizophrenia – SCZ; bipolar disorder – BPD; healthy controls – CNT) on regional brain grey matter (GM). F-values of clusters with significant differences ($p < 0.05$, FWE correction) are color coded and superimposed on template MNI space sections. *Bottom:* Boxplots of the distribution of total GM volume (ml) and GM volume in the right globus pallidus (ml) across participants in each group. There is no statistically significant difference between groups in total GM volume; *** indicates significant difference in the volume of globus pallidus in SCZ > CNT (post-hoc $p < 0.001$, Bonferroni corrected).

with more severe general psychopathology – BPRS – was also found (Pearson $r = 0.314$, $p = 0.048$) – results are shown in Fig. 4. Having explored the relation of gyrification with clinical data, we found a positive association between gyrification in the left BA40 and higher antipsychotic dosage – chlorpromazine equivalents – in BPD patients as a group (Spearman $\rho = 0.486$, $p = 0.030$). Analyzing both SCZ and BPD as a whole, higher gyrification in the left BA40 was associated with lower scores in the Schizo-Bipolar Scale (Spearman $\rho = -0.535$, $p < 0.001$) and higher functioning (Spearman $\rho = 0.358$, $p = 0.023$); gyrification in the right BA47 correlated negatively with CPZE – antipsychotics mean dosage (Spearman $\rho = -0.313$, $p = 0.049$). Results are presented in Fig. 4.

4. Discussion

The present work used a combined approach of conventional and novel brain morphometric measures to compare individuals with atypical SCZ or BPD syndromes in early years of disease. We found an increased volume of the right globus pallidus in patients with SCZ, divergent gyrification of the left supramarginal gyrus in BPD vs. SCZ, and decreased gyrification of the right inferior frontal gyrus in SCZ. Relevant associations between the imaging findings and psychopathological measures were also identified.

In line with previous studies, we observed an increase in the volume of the globus pallidus (GP) in SCZ patients even at early stages of disease. The design of our study allowed a relatively reduced time of

exposure to possible confounding factors, such as disease duration and antipsychotic treatment (van Erp et al., 2014). There is conflicting evidence on the impact of disease duration on the volume of deep grey matter, with some studies showing no effect (Fusar-Poli et al., 2013) whilst others demonstrated a positive association with bilateral GP volumes (Hashimoto et al., 2018). Although causality is uncertain, it might be hypothesized that such morphological changes were acquired rather than reflecting a neurodevelopmental nature.

Unlike atypical antipsychotics, classical antipsychotics have been associated with generalized reductions in GM volume but with an enlargement of the basal ganglia (Lang et al., 2004; Lieberman et al., 2005). This has been corroborated by a recent meta-analysis reporting that a daily dose of antipsychotics was positively associated with left GP volume and negatively with right hippocampus volume (Hashimoto et al., 2018). It was also associated positively with laterality index of globus pallidus, while the class of antipsychotics did not seem to modulate the effect on subcortical volume. Womer and colleagues also found increased GP and caudate volumes in psychotic patients (both SCZ and psychotic BPD), while non-psychotic BPD patients had the smallest volumes, even when compared with healthy controls (Womer et al., 2014). Findings of a larger globus pallidus and leftward asymmetry in globus pallidus volume were also reported by the EN-IGMA Schizophrenia working group (van Erp et al., 2014), and the Japanese consortium (COCORO - Cognitive Genetic Collaborative Research Organization), respectively (Okada et al., 2016).

In BPD patients, subcortical volumetric abnormalities have been

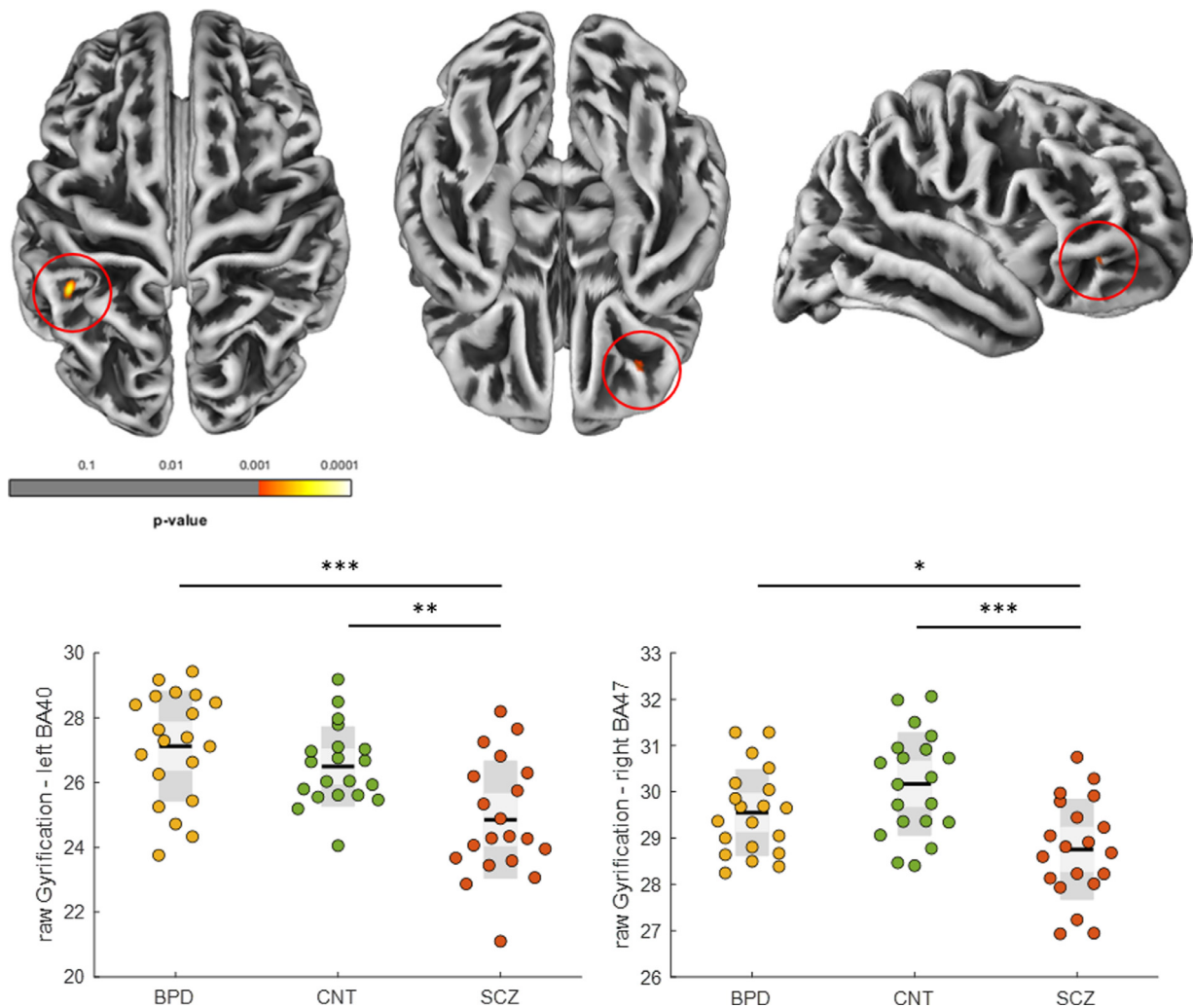


Fig. 3. Top: Surface-based morphometry analysis of group effects (schizophrenia – SCZ; bipolar disorder – BPD; healthy controls – CNT) on gyrification, corrected for age and gender. Group differences (thresholded at voxel level with $p < 0.001$ and corrected with cluster level non-stationary cluster extent) are highlighted with significance-levels visualized on a red to yellow scale and superimposed on a template reconstruction of brain surface in MNI space. An effect of group was found in gyrification in left supramarginal gyrus (top left) and right inferior frontal gyrus (top middle and right). Bottom: Boxplots of the distribution of gyrification in left supramarginal gyrus (BA40) and right inferior frontal gyrus (BA47) across participants in each group. Significant differences were found with the comparisons BPD > SCZ ($***p < 0.001$) and CNT > SCZ ($**p = 0.005$) in left BA40; and BPD > SCZ ($*p = 0.048$) and CNT > SCZ ($***p < 0.001$) in right BA47.

assessed in the ENIGMA Consortium, demonstrating the presence of enlarged lateral ventricles, and volume loss of the hippocampus and the thalamus. For all other subcortical structures, including the globus pallidus, no significant differences were identified vs. controls (Hibar et al., 2016). In summary, as demonstrated in our study, relatively well-controlled for confounding factors, the increased GP volume documented in SCZ is not consistently found in BPD patients adjusted for age and disease length.

Changes in gyrification found in our study should be interpreted in light of the currently limited knowledge on this innovative biomarker, in particular in populations with BPD. In SCZ, although more data are available, conflicting findings have been reported as evidenced by the presence of either hypo- or hyper-gyrification involving mostly prefrontal and temporal areas (Nanda et al., 2014; Spalthoff et al., 2018). It has been hypothesized that gyrification rests on early developmental disturbances, based on a smaller subset of brain areas showing developmental delay, while volumetric changes emerge only at later stages, such as prodromes or clinical onset (Spalthoff et al., 2018; Zilles et al., 2013).

Compared with healthy controls, we found increased gyrification of the left supramarginal gyrus (SMG – BA40) in patients with BPD and a

decreased gyrification of the SMG in patients with SCZ. Given that BPD and SCZ frequently share brain morphometric features (Ivleva et al., 2010), these contrasting findings are relevant, but appear to corroborate the results of other morphologic and functional imaging studies using classical volumetric and microstructural measures. In the EN-PACT study (European Network on Psychosis, Affective disorders and Cognitive Trajectory), the left SMG was one of the areas where grey matter volume loss was most significant in clinical samples of BPD and SCZ (Maggioni et al., 2017). In other studies it was observed a volume reduction of the right SMG in SCZ (Amann et al., 2016) or in both SCZ and, although at uncorrected level, BPD patients (Nenadic et al., 2015b). Concerning structural connectivity, reduced and increased fractional anisotropy were found in SCZ and BPD, respectively, with increased mean GM diffusion in both clinical samples (Anderson et al., 2013). A negative correlation was further identified between alexithymia and reduced volume of the left SMG in SCZ patients (Kubota et al., 2011). The SMG has been functionally associated with social cognition and Theory of Mind, namely its more early developing neural components (Saxe and Powell, 2006; Silani et al., 2013), and social cognition deficits have been proposed as the most significant predictors of functionality in patients with SCZ (Couture et al., 2006;

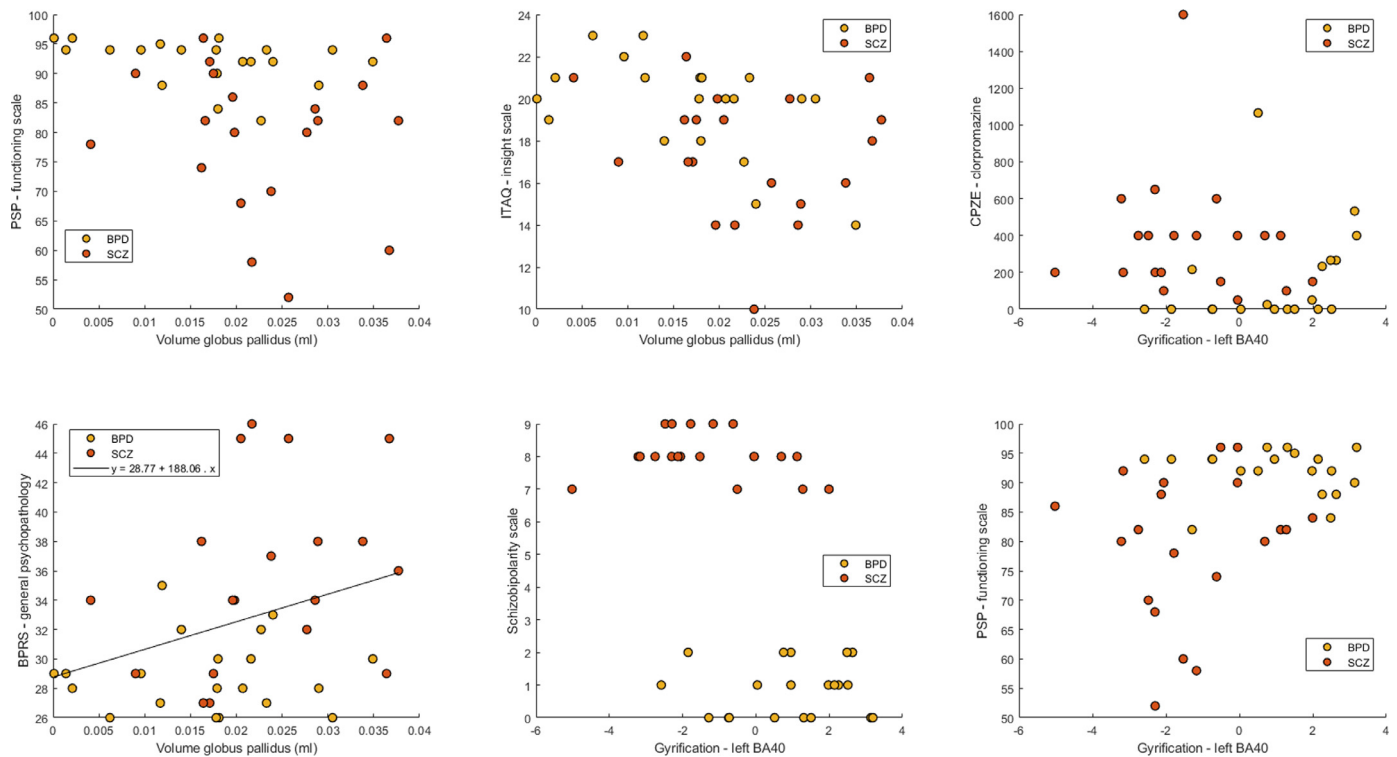


Fig. 4. Scatter plots of the distribution of compared imaging and clinical data across participants in each clinical group (schizophrenia – SCZ; bipolar disorder – BPD). Top left: GP volume and functioning (Spearman $\rho = -0.359$, $p = 0.023$); top center: GP volume and insight (Spearman $\rho = -0.420$, $p = 0.007$); top-right: gyrification in left BA40 and antipsychotic current dosage (Spearman $\rho = -0.313$, $p = 0.049$); bottom-left: GP volume and general psychopathology (Pearson $r = 0.314$, $p = 0.048$; the linear regression line is included only for this parametric relation); bottom-center: gyrification in left BA40 and Schizo-Bipolar scale score (Spearman $\rho = -0.535$, $p < 0.001$); bottom-right: gyrification in left BA40 and functioning (Spearman $\rho = 0.358$, $p = 0.023$).

Madeira et al., 2016).

Our study showed decreased gyrification of the right inferior frontal gyrus in schizophrenia, a finding that is corroborated by several functional neuroimaging studies. In a fMRI study of BPD and SCZ patients using a language-associated activation task, BPD patients engaged emotion processing brain areas more than healthy controls and individuals with SCZ, recruiting the right BA47 to a greater extent (McIntosh et al., 2008). Another fMRI study of euthymic BPD patients, performing an affective task paradigm involving matching and labeling of emotional facial expressions, reported reduced activation relative to healthy controls in the right BA47 (Foland-Ross et al., 2012). Irrespective of structural thinning in BPD patients, it has been hypothesized that the lateral section of the orbitofrontal cortex might suppress amygdala output via a projection from the medial section (Foland-Ross et al., 2011).

Our study represents an important contribution to the knowledge on gyrification in patients with BPD and SCZ, and unlike previous studies that focused on prefrontal gyrification our study assessed for the first time whole-brain gyrification (McIntosh et al., 2009; Nenadic et al., 2015). Nenadic and colleagues showed that BPD patients had increased local gyrification in the right anterior infragenu cingulate cortex compared to both SCZ and controls, and in left dorsolateral prefrontal compared to controls, whereas the SCZ group exhibited increased gyrification in the right anterior medial prefrontal cortex and orbitofrontal cortex compared with controls (Nenadic et al., 2015a). We found no gyrification differences of these regions in our sample, which could be explained by imbalances in gender and age distribution in their sample, as a larger proportion of male patients was found in the SCZ subsample, and BPD patients had higher age compared to the SCZ group (37.69 vs. 32.97 years). In our study, age and gender were well-balanced across the 3 groups, and its sample was younger and had shorter disease duration (5.2 and 6.0 years in BPD and SCZ) compared

to Nenadic's population (9.9 and 8.9 years, respectively), highlighting earlier disease-specific changes, while minimizing the potential influence of late unspecific processes. Age could also have influenced McIntosh and colleague's findings, given the higher mean-age of BPD and SCZ patients (39.6 and 38.0 years, respectively), although gender was balanced in both clinical groups and controls (McIntosh et al., 2009). While reduced prefrontal gyrification was reported in BPD patients, these results were less evident than in SCZ individuals and the parcellated gyrification index was calculated only in the ventral and dorsal prefrontal sub-regions, limiting the anatomical characterization. Also of note is that the clinical sample of that study was selected from multiplex families, with every patient having at least one relative with the same disorder, and thus limiting generalizability.

As described above, our study groups were gender-matched, which is particularly relevant when considering the hypothesis formulated by Timothy Crow that gender, interacting with laterality, might explain some of the structural variance between BPD and SCZ patients; this is supported by a recent meta-analysis (Bora et al., 2012; Crow et al., 2013; Nenadic et al., 2015b). Hemispheric lateralization of mood regulation has also been reported, suggesting that positive or appetitive-related emotions are lateralized towards the left, while negative or aversive-related emotions are right-hemisphere biased (Foland-Ross et al., 2011; Rotenberg, 2004). The relation of SCZ and BPD with brain lateralization provided context to the asymmetric findings of gyrification in our study. Differences regarding brain gyrification findings could reflect regional variation in the abnormalities of gyrification, with age, disease progression and neurodevelopmental factors, all influencing gyrification findings (Bo Cao et al., 2017; Palaniyappan et al., 2011). Of interest to our findings of asymmetric regional gyrification is a previous morphological study in SCZ (Palaniyappan et al., 2011) showing that patients had significant hypogyrification in most prefrontal regions. However the most striking

finding was that the normal left > right pattern of prefrontal gyrification was reversed in SCZ patients.

Long term challenges in differentiating schizophrenia from classic manic-depressive psychosis, now considered as type I Bipolar Disorder with psychotic features, suggest that common psychotic symptoms could be a unifying feature for biomarker research (Ivleva et al., 2017; Reininghaus et al., 2019). In fact, it has been hypothesized that gyrification changes, namely in frontal regions, could be a phenotypic core feature of psychotic disorders (Nenadic et al., 2015a). A study originated from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) consortium addressed gyrification in a sample of BPD, SCZ, schizoaffective (SZA) patients, patient relatives and healthy controls, using local gyrification index (Nanda et al., 2014). Significant regionally localized hypogyrification was reported in psychotic patients, particularly in the cingulate cortex. Interestingly, direct BPD-SCZ comparison yielded no significant results and SZA patients, a hypothetical intermediate disorder to SCZ and BPD, appeared to exhibit a pronounced profile of hypogyrification. Study strengths, besides the availability of unaffected patient relatives, included assessment of current medication, not only antipsychotic, but also lithium usage; lithium has been shown to influence the structure of the human brain, namely increasing GM volume (Lyoo et al., 2010; Moore et al., 2000). Of notice, only one of our study's BPD patients was medicated with lithium. Nonetheless, once again age and gender might have been limiting factors in the B-SNIP consortium study, with higher mean-ages, and dramatic differences in the latter variable: 64% male patients in the SCZ group, compared with 31% in the BPD sample, 47% of healthy controls and 29% of patient-relatives (Nanda et al., 2014).

Finally, when evaluating findings from different studies using a novel parameter such as gyrification measures, methodological questions are obviously relevant. Although gyrification is thought to be a stable marker, available open-source tools differ regarding labor intensity and computational demands. We used a solid option that has been validated in clinical settings – CAT12 – and is considered both fast and reliable (Righart et al., 2017; Seiger et al., 2018). Furthermore, gyrification values estimated with the commonly used FreeSurfer have a higher rater-dependency than those estimated with the curvature approach in CAT12, making this an easy-to-use alternative approach.

Despite our study's stringent design, namely inclusion/exclusion criteria and matching for relevant variables such as age and gender, some limitations should be discussed. The study's cross-sectional nature hinders the investigation of specific disease trajectories, that only longitudinal data might clarify (Cao et al., 2017). The relatively small sample size, namely of particular subgroups such as non-psychotic BPD patients (only 20% of the BPD group), precludes the assessment of some variables, e.g. the influence of psychotic symptoms on BPD morphometric changes. While we assessed and controlled for current medication use, namely antipsychotics, its possible effect as a confounder (e.g. cumulative usage of antipsychotics) cannot be entirely ruled out.

5. Conclusions

A perceived feature of psychiatric neuroimaging research over the past two decades has been its relative disconnection from real-world clinical care and its unmet needs (Etkin, 2019). While MRI classification studies using traditional GM measures have shown some promising results in accurately separating individuals suffering from SCZ and BPD (Schnack et al., 2014), brain imaging biomarkers would be more clinically useful in earlier phases of disease, where these two disorders can be hard to differentiate.

In this brain MRI comparison study of individuals with SCZ or BPD in their first years of disease, we found an increased volume of the right globus pallidus as a consistent marker in SCZ, but not BPD, when evaluating traditional MRI measures. On the other hand, gyrification was found to be differentially changed between clinical groups, diverging from healthy controls in different directions in the left SMG gyrus,

and in the same direction, but with different strength, in the right inferior frontal gyrus. The findings involving the left SMG gyrus are of particular interest, given this contrasting pattern found in two disorders that frequently share morphometric and genetic features (Ivleva et al., 2010).

Gyrification analysis, an innovative and biologically plausible approach, could aid identification of biomarkers relevant to different aspects of pathophysiology in SCZ and BPD. Studies using these innovative morphometric features in early stage patients' data could enlighten specific disease trajectories, identifying distinct psychopathological phenotypes and its core neurobiological processes, perhaps generating helpful biomarkers for clinical practice, favoring earlier diagnosis and improving treatment selection.

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CRediT authorship contribution statement

Nuno Madeira: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Project administration. **Joao Valente Duarte:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Visualization. **Ricardo Martins:** Validation, Formal analysis, Investigation, Resources, Data curation, Writing - review & editing. **Gabriel Nascimento Costa:** Investigation, Resources, Writing - review & editing. **António Macedo:** Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration. **Miguel Castelo-Branco:** Conceptualization, Methodology, Resources, Writing - original draft, Supervision, Project administration, Funding acquisition.

Declarations of Competing Interest

The authors have no conflict of interest to report.

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