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Insula volumes in first-episode and chronic psychosis: A longitudinal MRI study

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ABSTRACT

Background: Alterations in insular grey matter (GM) volume has been consistently reported for affective and non-affective psychoses both in chronic and first-episode patients, ultimately suggesting that the insula might represent a good region to study in order to assess the longitudinal course of psychotic disorders. Therefore, in this longitudinal Magnetic Resonance Imaging (MRI) study, we aimed at further investigating the key role of insular volumes in psychosis.

Material and Methods: 68 First-Episode Psychosis (FEP) patients, 68 patients with Schizophrenia (SCZ), 47 Bipolar Disorder (BD) patients, and 94 Healthy Controls (HC) were enrolled and underwent a 1.5 T MRI evaluation. A subsample of 99 subjects (10 HC, 23 BD, 29 SCZ, 37 FEP) was rescanned after 2,53 ± 1,68 years. The insular cortex was manually traced and then divided into an anterior and posterior portion. Group and correlation analyses were then performed both at baseline and at follow-up.

Results: At baseline, greater anterior and lower posterior insular GM volumes were observed in chronic patients. At follow-up, we found that FEP patients had a significant GM volume increase from baseline to follow-up, especially in the posterior insula whereas chronic patients showed a relative stability. Finally, significant negative correlations between illness severity and pharmacological treatment and insular GM volumes were observed in the whole group of psychotic patients.

Conclusions: The longitudinal assessment of both chronic and first-episode patients allowed us to detect a complex pattern of GM abnormalities in selective sub-portions of insular volumes, ultimately suggesting that this structure could represent a key biological marker of psychotic disorders.

1. Introduction

The diagnosis and clinical management of major mental disorders are still founded on psychopathological knowledge (Carvalho et al., 2020), causing delays in the diagnostic process and treatment definition, which in turn determines diagnostic uncertainty and lack of reliability on early clinical interventions. Identification of objective biomarkers would help differentiate more specific diagnostic groups and would facilitate the definition of therapeutic approaches, therefore delivering more tailored interventions (Dusi et al., 2017; Pigoni et al., 2019).

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In particular, first episode psychoses (FEP) often undergo a long follow-up period before a stable diagnosis and treatment are defined (McGorry, 2015). In this context, magnetic resonance imaging (MRI) can offer a practical tool for a better characterization of FEP patients and a deeper investigation of the neurobiological processes determining their psychopathology (Calvo et al., 2019; Rokicki et al., 2021). In particular, structural MRI studies provided key evidence that could orient clinicians toward a differentiation between affective and non-affective psychoses, already at the early stages of illness (Satterthwaite et al., 2016).

Interestingly, when a stable diagnosis is reached, both bipolar disorder (BD) and schizophrenia (SCZ) patients show grey matter (GM) abnormalities, with SCZ usually presenting more severe alterations, especially in prefrontal and temporal areas and in subcortical regions, such as the insula, thalamus, and amygdala (Maggioni et al., 2017). Although the progression of these changes during the illness history has not yet been completely understood, GM alterations have been found to be associated with the age of onset (Pina-Camacho et al., 2016; Torres et al., 2016), the number of hospitalizations, and illness severity (Rosa et al., 2015; Vita et al., 2012). These suggest that a remitting-relapsing course might negatively affect brain measures, as well as the duration of antipsychotic treatment (Hashimoto et al., 2018; Vita et al., 2015). However, the effect of these factors on the brain is still difficult to disentangle from the standard progression of the disorders, and therefore the employment of FEP patients with little or no pharmacological treatment might be paramount to identifying the putative brain alterations associated with psychosis, and to at least partially reduce the effect of the described confounders.

In an effort to identify common patterns, rather than differences across main psychiatric diagnoses, the insula and anterior cingulate cortices were consistently found to be altered in both the BD and SCZ (Goodkind et al., 2015), as well as in FEP patients (Díaz-Caneja et al., 2019) and subjects at high risk for psychosis (Chung et al., 2019). The patients usually show GM reductions in these regions compared to controls.

Specifically for the insula, this structure is a paralimbic multimodal cortical region that is highly connected to frontal, parietal and temporal lobes, limbic structures, and other subcortical areas, such as the caudate nucleus, the putamen, and the thalamus (Ferenczi et al., 2016; Leong et al., 2021). While the posterior insula is involved in the modulation of external and interoceptive stimuli, the anterior insula is responsible for the integration between internal and external inputs and cognitive and emotional responses, through its connections with the anterior cingulate, the prefrontal cortex, and the amygdala (Ferenczi et al., 2016; Leong et al., 2021). Thus, this area might be a putative target for identifying early brain alterations among FEP compared to stabilized SCZ and BD patients. However, the trajectories of insular volume in patients with both affective and non-affective illnesses have not been defined yet, and to the best of our knowledge, a direct longitudinal comparison between FEP, BD and, SCZ patients and healthy controls (HC) on insular volume has not been performed yet.

Therefore, in this study, we followed up for ≃3 years, three populations of patients with FEP, SCZ, and BD and one group of HC. Insular volume was measured longitudinally with the final aim of understanding the role of this brain area in the development of psychosis, in its early and chronic stages. Specifically, we will explore a) differences in insula GM volumes at baseline between patients and HC, b) the progression of GM changes in the insular subregions from baseline to follow-up, to model specific disease trajectories associated with diagnoses, and c) whether clinical and demographic variables are associated with GM modifications over the follow-up period, to try to disentangle the effects of such confounders from the standard progression of psychotic disorders. Our main hypothesis is that chronic BD or SCZ patients will show significant insular volume differences at baseline compared to FEP patients that will likely reduce at follow-up, given that the most prominent brain modifications tend to occur in the first years of the disease (Vita et al., 2012). Finally, we also hypothesized the presence of different and unique volumetric trajectories for affective and non-affective psychoses.

2. Methods

2.1. Participants

The sample included 68 FEP patients, 68 patients with SCZ, 47 BD patients and, 94 HC. FEP patients were recruited as participants in the PICOS project (Psychosis Incident Cohort Outcome Study) (For more details about the project, please refer to our prior publications (Lasalvia et al., 2012; Squarcina et al., 2015) and the Supplementary Materials).

Patients with SCZ and BD were recruited through the South-Verona Psychiatric Case Register (PCR) (Ferro et al., 2017), within the FIRST project (please refer to our previous publication (Enrico et al., 2021). For all patients, a formal ICD-10 diagnosis was obtained and confirmed by the item group checklist (IGC) of the Schedule for clinical assessment in neuropsychiatry (SCAN). Exclusion criteria were: (1) comorbid axis I psychiatric disorders, (2) alcohol or substance abuse within the 6 months prior to MRI, (3) history of traumatic head injury with loss of consciousness, (4) major neurological medical illnesses, or (5) mental retardation.

HC were recruited through word of mouth and advertisements in the geographically defined catchment area of South Verona. They had no history of head injury or psychiatric disorder, this was determined by using a brief modified version of the Structured Clinical Interview - Nonpatient version (First et al., 2002), no history of psychiatric disorder among first-degree relatives, no history of alcohol or substance misuse, and no current major medical illness.

At baseline, all subjects underwent a 1.5 T MRI evaluation and 99 subjects (10 HC, 23 BD, 29 SCZ, 37 FEP) were rescanned a second time after a mean time of 2,53 ± 1,68 years. All subjects signed informed consent and the PICOS and FIRST projects were approved by the ethics committees of the coordinating center (Azienda Ospedaliera Universitaria di Verona; PICOS [registration n: 1103], FIRST [registration n: 954]). The clinical symptomatology of all patients was evaluated using the 24 item Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). An assessment of the day-life impact of mental diseases was performed with the Global Assessment of Functioning Scale (GAF) (Endicott, 1976). Data on pharmacological treatment was collected for all patients. The demographic and clinical details of all the subjects at baseline and follow-up are presented in Tables 1 and 2, respectively.

2.2. MRI procedure

MRI scans were acquired with a 1.5-T Siemens Magnetom Symphony Maestro Class, Syngo MR 2002B, at the Borgo Roma University Hospital of Verona. Please refer to the Supplementary Materials with all the details about our acquisition parameters.

2.3. Image analysis

All imaging data were analyzed using the BRAINS2 software (Magnotta et al., 2002). The region of interest (ROI) of bilateral insular cortices was defined according to previously published criteria (Kasai et al., 2003). The manual tracing was performed in a coronal view (Fig. 1). A detailed description of the ROI tracing is reported in the Supplementary Materials.

2.4. Statistical analysis

Statistical analyses were conducted using the R software (https://www.R-project.org). Demographic and clinical variables were compared using Pearson's chi-square and one-way analysis of variance (ANOVA), where appropriate. We used a multiple testing correction method for structured hypotheses for the analysis of insular volumes,

Table 1
Descriptive statistics of the baseline sample.

	Healthy controls (N = 94)	SCZ patients (N 68)	BD patients (N 47)	FEP patients (N68)	Statistics	
Age (years), range (min–max)	38.66 ± 11.53 (20–61)	39.36 ± 11.92 (18–62)	47.78 ± 9.53 (27–64)	30.64 ± 9.19 (18–64)	$F_{3.273} = 23.76$	**p < 0.001**
Gender: M/F	48/46	44/24	17/30	38/30	$\chi^2_3 = 9.45$	**p = 0.024**
Ethnicity	Caucasian (all)	Caucasian (all)	Caucasian (all)	Caucasian (65) Asian (3)		
Handedness (% right)	80.0 %	84.62 %	95.35%	80. 0 %	$\chi^2_3 = 5.8$	**p = 0.123**
BPRS total score		43.38 ± 16.89 (N 58)	31.29 ± 6.88 (N 17)	30.64 ± 8.87 (N 59)	$F_{2.131} = 15.83$	**p < 0.001**
BPRS- Negative symptoms		11.20 ± 4.00 (N 58)	4.78 ± 3,58 (N 40)	8.62 ± 2.77 (N 60)	$F_{2.155} = 40.62$	**p < 0.001**
BPRS-Positive symptoms		11.07 ± 6.26 (N 58)	6.94 ± 3.11 (N 17)	6.34 ± 1.93 (N 59)	$F_{2.131} = 17.68$	**p < 0.001**
GAF scores	77.18 ± 5.46 (N 81)	52.46 ± 11.83 (N 60)	58.39 ± 11.96 (N 41)	60.52 ± 17.20 (N 57)	$F_{3.235} = 57.11$	**p < 0.001**
Atypical antipsychotics (YES/NO)	0/93	44/24	19/27	3/63	$\chi^2_3 = 111.82$	**p < 0.001**
Typical antipsychotics (YES/NO)	0/93	24/44	9/37	5/62	$\chi^2_3 = 44.658$	**p < 0.001**
Mood stabilizers (YES/NO)	0/93	24/44	9/37	5/62	$\chi^2_3 = 44.658$	**p < 0.001**

BD, Bipolar Disorder, BPRS, Brief Psychiatry Rating Scale, FEP, First-Episode Psychosis, GAF, Global Assessment of Functioning, SCZ, Schizophrenia.

Table 2
Descriptive statistics of the follow-up sample.

	Healthy controls (N = 10)	SCZ patients (N 28)	BD patients (N 23)	FEP patients (N 38)	Statistics	
Age (years), range (min–max)	39.40 ± 12.13 (22–57)	44.21 ± 11.23 (22–65)	50.65 ± 8.75 (33–65)	33.14 ± 9.48 (20–54)	$F_{3.95} = 14.47$	**p < 0.001**
Gender: M/F	2/8	20/9	7/16	22/15	$\chi^2_3 = 12.539$	**p = 0.005**
Ethnicity	Caucasian (all)	Caucasian (all)	Caucasian (all)	Caucasian (37) Asian (1)		
Handedness (% right)	66.6%	90 %	94.74%	75.68%	$\chi 2 = 5.99$	**p = 0.11**
BPRS total score		38.06 ± 9.38 (N 16)	27 ± 5.2 (N 3)	28.86 ± 4.84 (N 36)	$F_{2.52} = 11.85$	**p < 0.001**
BPRS-Negative symptoms		10.2 ± 2.52 (N 16)	4 ± 5.19 (N 19)	7.78 ± 1.33 (N 36)	$F_{2.68} = 18.79$	**p < 0.001**
BPRS-Positive symptoms		5.78 ± 4.79 (N 23)	7.33 ± 4.04 (N 3)	5.97 ± 1.61 (N 36)	$F_{2.59} = 0.3$	**p = 0.742**
GAF scores	79 ± 6.45 (4 missing)	48.11 ± 12.89 (0 missing)	62.22 ± 13.9 (N 22)	61.57 ± 13.38 (N 37)	$F_{3.89} = 12.09$	**p < 0.001**
Atypical antipsychotics (YES/NO)	0/10	17/11	7/16	1/36	$\chi^2_3 = 29.863$	**p < 0.001**
Typical antipsychotics (YES/NO)	0/10	10/18	4/19	4/33	$\chi^2_3 = 8.0913$	**p = 0.042**
Mood stabilizers (YES/NO)	0/10	0/27	14/7	2/2	$\chi^2_3 = 29.633$	**p < 0.001**

BD, Bipolar Disorder, BPRS, Brief Psychiatry Rating Scale, FEP, First-Episode Psychosis, GAF, Global Assessment of Functioning, SCZ, Schizophrenia.

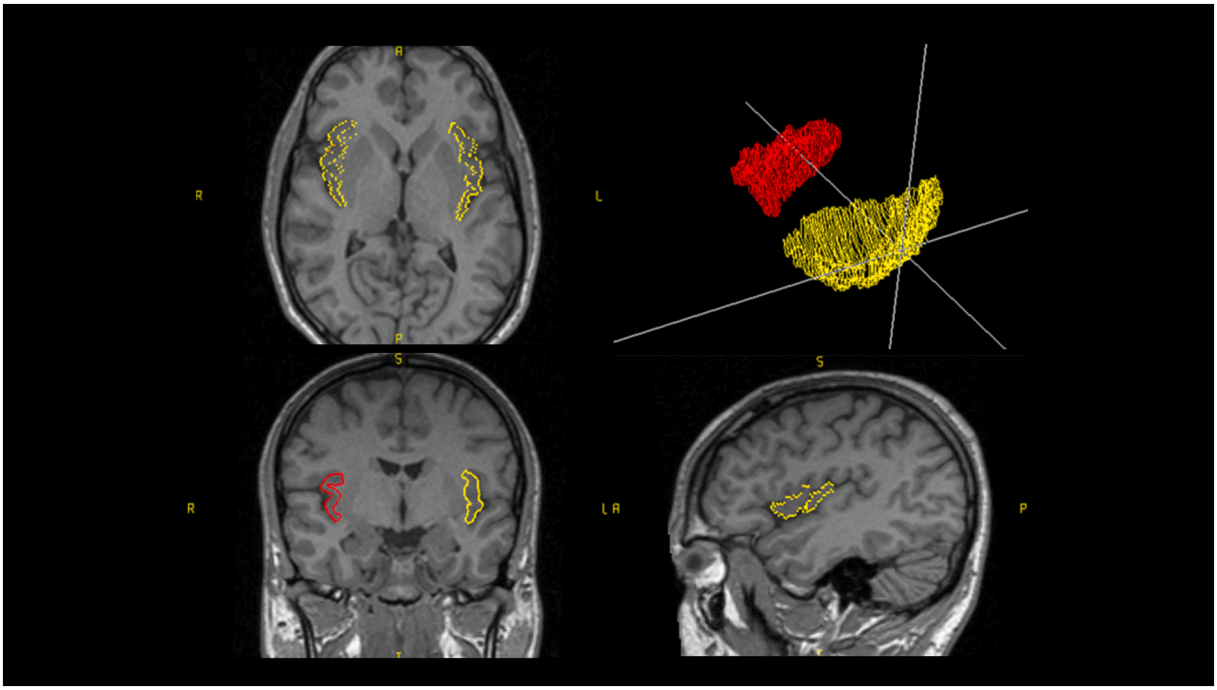

Fig. 1. ROI tracing of insular volume with its 3D reconstruction.

called the inheritance procedure (Goeman and Finos, 2012). Briefly, the Inheritance Procedure guarantees the familywise error rate (FWER) at level $\alpha = 0.05$ in multiple testing analyses, i.e., 3 MANOVAs. Firstly, the procedure applied multivariate analysis of variance (MANOVA) test, using insula volumes (i.e., left/right anterior/posterior) as response variables; diagnostic groups, such as age, gender, handedness, and total intracranial volumes were used as covariates. If the multivariate analyses for diagnostic groups were significant at a significance level of p =

0.05, two MANOVAs were fitted, one for the anterior insula and one for the posterior insula. The significance level was then set at $p = 0.05/2 = 0.025$. When an area results significantly, each sub-area was used as the dependent variable in a linear model. If the diagnostic group covariate was significant at level $p = 0.05/K$, where K equals the number of MANOVAs found significant, post-hoc analysis with Holm correction was performed for the four diagnostic groups. In addition, we adjusted for multiple comparisons using the Holm method and for multiple testing using the Bonferroni correction by setting the significance level at $p = 0.05/K$, since K regressions have been performed.

For the longitudinal changes in volumes, the same method was applied, using as a dependent variable the delta volumes (ΔV) of each part of the insula, i.e., insula volume at T1 – insula volume at T0. Finally, correlations between sociodemographic (i.e., age) or clinical features (i.e., Global Assessment of Functioning (GAF), Brief Psychiatry Rating Scale (BPRS), length of illness, antipsychotics lifetime, pharmacological treatment, and ΔV of the four insular portions at baseline and follow-up were carried out by an ANOVA based on a linear model, with age and gender as covariates; Bonferroni correction was applied. In addition, Cohen's f was computed for measuring the effect and size of the regression with the following interpretation: small (0.02), medium (0.15), and large (0.35).

For all analyses, the coefficients representing the predicted values of the insular volumes for each group after controlling for all the covariates have been shown in Figs. 2–5. Finally, the distributions of the insular volumes (reported in the Supplementary Materials) were not perfectly normal but the analysis of the residuals validated the regression model used.

3. Results

3.1. Baseline

Baseline results are shown in Fig. 2. Since the first step MANOVA was significant ($F(12, 737) = 12.488$, $p < 0.001$), a second step MANOVA was performed and was also found significant for both insula portions (anterior insula GM, $F(6, 490) = 4.512$, $p < 0.001$; posterior insula GM, ($F(6, 490) = 26.517$, $p < 0.001$)). Subsequently, a linear regression was carried out with each subdivision of insular GM volume – anterior left, anterior right, posterior left, posterior right – as the dependent variable and the diagnostic groups, age, gender handedness, and total intracranial volumes as covariates. Then, for each significant linear model, a post-hoc analysis with Holm correction for multiple comparisons was performed. It revealed statistically significant differences in left anterior insular GM volume in HC vs SCZ ($t = 4.305$, $p < 0.001$), and HC vs BD ($t = 3.863$, $p = 0.003$) with greater volume in the patients' group, as well as in FEP vs SCZ ($t = 3.353$, $p = 0.02$) with greater volume in the FEP group.

Significant differences were found in right anterior insular GM volume between HC and SCZ ($t = 4.08$, $p = 0.001$), with patients having greater volume. Analyzing the left posterior insular GM volume, significant differences were found between HC vs SCZ ($t = -11.263$, $p < 0.001$), HC vs BD ($t = -8.813$, $p < 0.001$), FEP and SCZ ($t = -10.27$, $p < 0.001$) and FEP and BD ($t = -7.226$, $p < 0.001$), with HC and FEP having lower GM volumes. Finally, in the right posterior insular GM volume significant differences were found between HC and SCZ ($t = -10.018$, $p < 0.001$), HC and BD ($t = -5.863$, $p < 0.001$) with patients having lower GM volumes, and between FEP and SCZ ($t = -7.162$, $p < 0.001$), FEP and BD ($t = -3.614$, $p = 0.007$), with FEP having lower GM volumes.

3.2. Longitudinal analysis

The longitudinal analysis replicated the multi-step procedure of the baseline analyses using as dependent variables the volumetric change (ΔV) parameters. Longitudinal results are shown in Fig. 3.

In addition, in this case, since the first step MANOVA was significant ($F(12, 210) = 6.721$, $p < 0.001$), a second step MANOVA was carried out. The MANOVA reached statistical significance only for the posterior insula ($F(6,142) = 15.614$, $p < 0.001$). Therefore, linear regression analyses were performed only for the two posterior insular regions (posterior left and posterior right). Then, post-hoc analysis with Holm correction for multiple comparisons was performed for each significant linear model. Post-hoc analyses revealed statistically significant differences in left posterior insula GM ΔV, with greater values in FEP compared to BD ($t = 11.013$, $p < 0.001$) and to SCZ ($t = 12.174$, $p < 0.001$) as well as between HC vs SCZ ($t = 8.017$, $p < 0.001$) and HC vs BD ($t = 6.749$, $p < 0.001$), with patients having greater ΔV. Further, statistically significant differences were observed in right posterior insula ΔV, with greater values in HC compared to both SCZ ($t = 3.526$, $p = 0.007$) and BD ($t = 2.974$, $p = 0.038$) as well as between FEP vs SCZ ($t =$

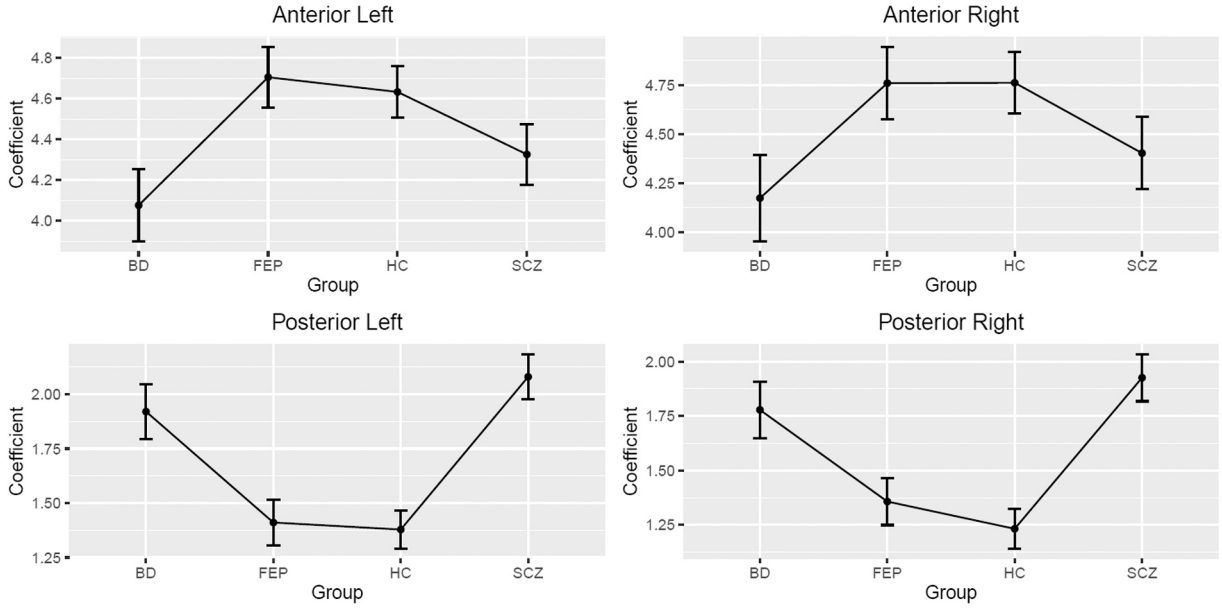

Fig. 2. Significant mean differences in grey matter volumes of insular subportions at baseline between patients with bipolar disorder (BD), schizophrenia (SCZ), first-episode psychosis (FEP) and healthy controls (HC).

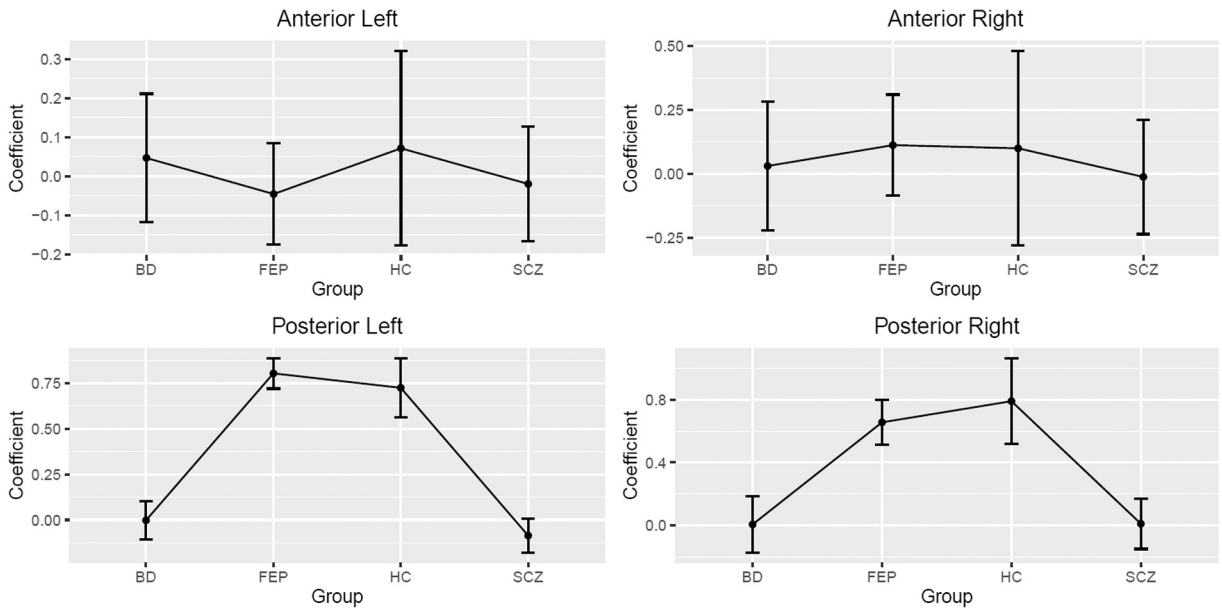

Fig. 3. Significant mean differences in ΔV of insular subportions between patients with bipolar disorder (BD), schizophrenia (SCZ), first-episode psychosis (FEP) and healthy controls (HC).

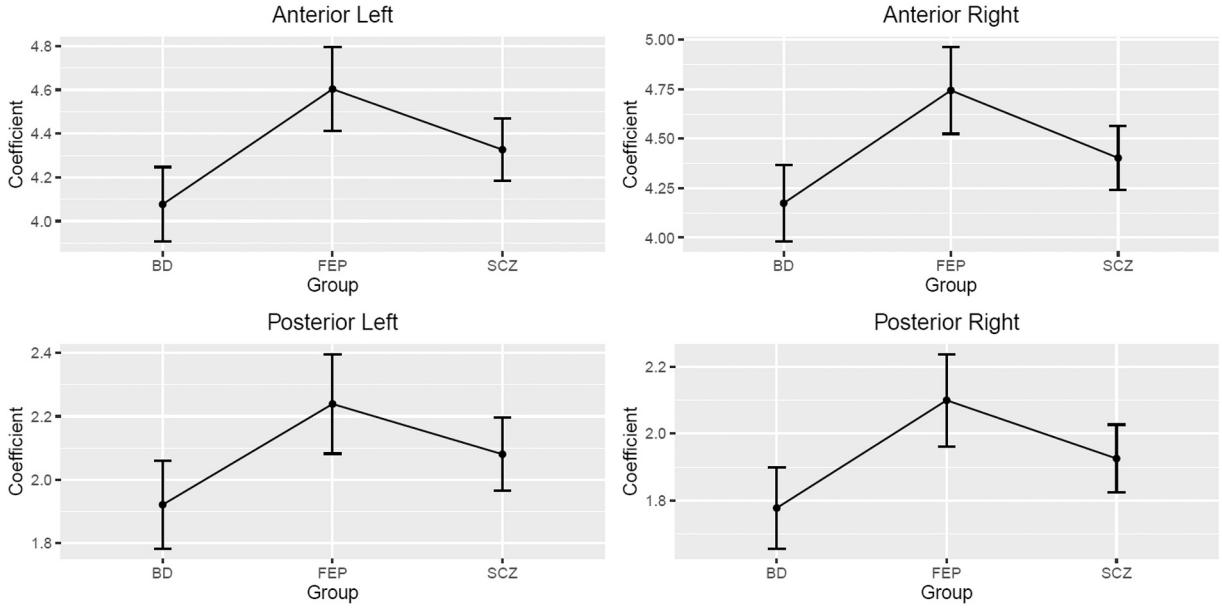

Fig. 4. Significant mean differences in insular volumes between patients with bipolar disorder (BD), schizophrenia (SCZ) and first-episode psychosis (FEP), where FEP volumes refer to T1 and SCZ/BD volumes refer to T0.

4.653, p = 0.002) and FEP vs BD (t = 4.108, p = 0.001), with FEP having greater ΔV.

3.3. Additional analysis

The multi-step procedure was applied to analyze the difference in insular GM volumes between FEP at follow-up and SCZ/BD at baseline. The results are shown in Fig. 4.

Since the first step MANOVA was significant (F (8, 268) = 3.336, p = 0.001), the second step was performed. The MANOVA reached statistical significance for the anterior insula (F (4, 272) = 3.123, p = 0.031), and for posterior insula (F (4, 272) = 3.355, p = 0.02). Therefore, the four linear regressions were carried out, one for each insular GM volume. The post-hoc analysis found a significant difference between FEP and BD (t = -3.013, p = 0.034) in the left anterior region, with FEP having greater volumes. Finally, a significant difference was found between FEP and BD in the right posterior insula volumes (t = -3.562, p = 0.006) with FEP having greater volumes. No differences have been observed in any of the other insular regions.

The same multi-step procedure was performed to study the differences in the volumetric change (ΔV) parameters between affective and non-affective FEP patients. The MANOVA with the ΔV of GM of the four insular portions (left, right, anterior, posterior) as dependent variables, and diagnostic groups, age, gender, handedness, and total intracranial volumes as covariates were not significant (F (4,64) = 0.663, p = 0.619). Moreover, we also investigated the differences in insular GM volumes, both at baseline and by using the volumetric change (ΔV) parameters, between the whole group of patients with affective (BD and affective

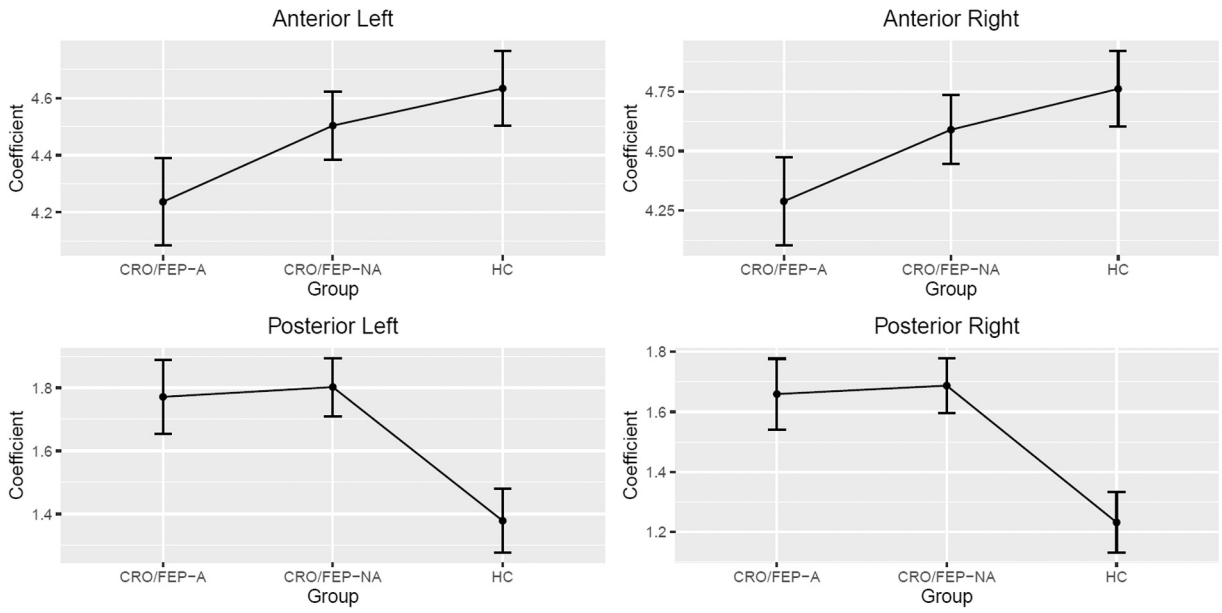

Fig. 5. Significant mean differences in grey matter volumes of insular subportions at baseline between patients with affective psychoses (CRO/FEP-A), non-affective psychoses (CRO/FEP-NA) and healthy controls (HC).

FEP) and non-affective (SCZ and non-affective FEP) psychosis using the same multi-step procedure (Fig. 5). Analyzing the four insular GM volumes at baseline, the group covariate in the first MANOVA was significant ($F(8,488)$, $p < 0.001$), as well as considering only the left volumes ($F(4,492)$, $p = 0.005$) and the right volumes ($F(4,492)$, $p < 0.001$) whereas by using the ΔV parameters as dependent variables, no significant differences were observed ($F(8, 140)$, $p = 0.09$). Therefore, the four linear regression analyses only for the baseline results were performed. The results showed a significant difference between HC and patients with affective psychoses in all four portions of the insula (left anterior ($t = 3.199$, $p = 0.01$), right anterior ($t = 3.077$, $p = 0.026$), with patients showing lower GM volumes compared to HC, and left posterior ($t = -4.923$, $p < 0.001$), and right posterior ($t = -6.697$, $p < 0.001$)), with patients showing lower GM volumes compared to HC. In addition, we found significant differences in the posterior insula bilaterally between HC and patients with non-affective psychoses (left ($t = -6.697$, $p < 0.001$), right ($t = -7.398$, $p < 0.001$)), with patients having higher GM volumes compared to HC, and in the right ($t = 3.214$, $p = 0.017$) and left ($t = 3.119$, $p = 0.023$) anterior insula. Finally, significant correlations between clinical/sociodemographic features and pharmacological treatment and insular GM volumes were also observed and reported in the Supplementary Results.

4. Discussion

In this study, we examined insular volumes in patients with a diagnosis of SCZ, BD, FEP, and in a group of HC both at baseline and at follow-up, to assess whether this region might represent a valid marker for the progression of distinct psychotic disorders. A complex pattern of GM modifications was observed both at baseline and follow-up. Specifically, at baseline, chronic patients showed increased GM volumes in both anterior and left posterior portions of the insula, as well as a reduced GM volume in the right posterior portion compared to HC. Moreover, FEP had steeper baseline-to-follow-up modifications, reaching the baseline volumes of SCZ patients, with opposite directions for anterior and posterior portions of the insula. Finally, significant correlations between insula GM volumes and age, antipsychotic medication, as well as a clinical and functioning measure were detected.

4.1. Baseline results

Results at baseline partially confirmed the available literature, suggesting that the insula can be regarded as one of the most affected regions in psychosis (Gupta et al., 2015; Nelson et al., 2020). Specifically, similar to our findings, recent studies also reported that the insula was found reduced in patients affected by SCZ (Gupta et al., 2015; Nelson et al., 2020) and BD (Choi et al., 2020) as well as in FEP patients (Escarti et al., 2019; Jung et al., 2019), although to a lesser extent compared to SCZ and BD.

In our sample, increased GM volumes in a sub-portion of the insula in chronic patients with both affective and non-affective psychosis were reported. Although this might be surprising at a first glance, it is now widely recognized that both SCZ and BD are not only characterized by a reduction in GM volumes but by more complex patterns of alterations (Chand et al., 2020; Voineskos et al., 2020). Indeed, recent studies (Voineskos et al., 2020) have also suggested that biological heterogeneity is a characteristic of SCZ and psychotic disorders, which can be overcome by finer parcellations of GM or by overcoming average differences as with recent machine learning studies (Chand et al., 2020; Pigoni et al., 2021).

It is important to highlight that the majority of previous neuroimaging studies on insular volumes have treated this structure as a single, homogeneous region, or have only considered its anterior part (Choi et al., 2020; Gupta et al., 2015). In contrast, in our sample, we explored both the anterior and posterior insula, highlighting a different pattern of increased and decreased GM modification, as also reported by a recent study on SCZ (Tian et al., 2019). Interestingly, our results seem in line with a recent study suggesting a different involvement of insular subregions and a differential association of these subregions to both clinical and cognitive aspects in psychotic patients (Sheffield et al., 2021). Although the causes of this differential alteration of insular GM are not easy to draw, some possibilities may be considered in the context of the existing literature showing that anterior and posterior insula are part of different networks subserving different functions (Li et al., 2019). Specifically, the anterior insula is a key hub of the salience network, which is often found altered in psychosis (Liang et al., 2021), possibly due to a persistent hyperdopaminergic state (Saviola et al., 2021), which leads the psychotic brain to a misleading assignment of object's salience. Therefore, it is not surprising that aberrant connectivity between the

anterior portion of the insula and temporal areas was found to be associated with auditory hallucinations (Chen et al., 2020; Yang et al., 2020) and negative symptoms (Sheffield et al., 2020) in SCZ, ultimately suggesting that this region might be a key functional area in psychotic disorders.

On the other hand, the posterior region is functionally connected with primary and secondary somatomotor cortices, parieto-temporo-occipital lobe, and motor regions of the cerebellum (Tian et al., 2019). Although the literature regarding this specific subregion is sparse in psychiatry, a recent study reported a significant association between the posterior insula and measures of impulsivity in patients affected by BD (Lois et al., 2020), therefore also suggesting that this portion of the insula might play a role in psychiatric disorders. Of note, in the last few years, some studies suggested that these two subregions might be altered in different and opposite ways in psychosis and clinical high-risk patients (Li et al., 2019; Tian et al., 2019). Specifically, Tian et al. (2019) reported an enlargement of the posterior insula and a shrinkage of the anterior insula in patients with SCZ, as also reported by our study. The causes and implications of these divergent alterations for psychotic disorders are not clear but could be related to the disrupted dopaminergic tone at the basis of psychoses (Saviola et al., 2021) that lead to an "overstimulation" of some areas compared to others. Additionally, a recent study (Rössler et al., 2020) showed that psychotic-like experiences are associated with functional disruption of dopamine afferents to the anterior insula, which is considered one of the possible causes of both affective and non-affective psychosis (McCutcheon et al., 2020). Therefore, this mixed picture of increased and decreased GM volumes seems to further support the hypothesis that the anterior and posterior insula are differently altered in psychotic disorders, possibly because they subserve different functions.

Interestingly, in our samples, such alterations are not present in the FEP group at baseline. This finding might be related to several factors. One of the possible reasons could be related to the fact that GM differences in FEP might still be subtle and not clearly evident from group-level analyses (Calvo et al., 2019; Tordesillas-Gutierrez et al., 2015) since they are less affected by the illness duration and long-term treatments (Hashimoto et al., 2018; Tomelleri et al., 2009). Moreover, differences in demographic and clinical features might also explain the differences between FEP and SCZ/BD at baseline. Indeed, age is known to affect GM both in healthy subjects and in the clinical population (Delvecchio et al., 2021) and similar influences have also been described for the duration of illness (Smieskova et al., 2012). These aspects have been further confirmed by our findings, which showed an overall negative influence of age on the anterior portion of the insula (see Supplementary Materials). Moreover, given the nature of our study, FEP patients are significantly younger and have a shorter duration of illness, and the cumulative effect of these variables on GM might not be clearly visible at baseline. Similarly, the different exposures to psychotropic drugs on GM volumes should also be considered, since chronic patients have been treated for significantly longer periods. Even though evidence on the effects of antipsychotic therapy on insula GM volumes in patients with SCZ and BD are still mixed (Roiz-Santiañez et al., 2015), a significant correlation between antipsychotic treatment and insular volumes was observed in our sample (see Supplementary Materials), therefore supporting the hypothesis that different treatments' duration and dosage might partially explain the negative findings observed in FEP at baseline.

4.2. Longitudinal results

Longitudinal results showed steeper modifications in insular GM volumes in FEP compared to chronic patients, with FEP reaching the baseline volumes of SCZ patients in most subregions.

This finding seems to be in line with previous literature reporting progressive GM changes characterizing psychotic disorders mostly occurring during the first years after the onset (Vita et al., 2012). However, there is considerable dispute as to whether such progressive brain changes are invariably present or are associated with and modulated by specific factors, such as symptoms, clinical outcome, antipsychotic treatments, and comorbidity (Zipursky et al., 2013) as well as age and age of onset (Pina-Camacho et al., 2016; Torres et al., 2016). In more detail, it has been consistently reported that while chronic older patients showed on average more widespread GM and WM abnormalities in various cortical and subcortical regions (Morimoto et al., 2021; Torres et al., 2016), brain alterations in FEP patients were found to be usually subtle when compared to healthy individuals (Pigoni et al., 2021; Torres et al., 2016). Also, it has been demonstrated that the trajectories of GM deficits seem to be influenced by an early age of onset in both affective and non-affective psychoses (Pina-Camacho et al., 2016; Torres et al., 2016).

Moreover, recent studies (Rosa et al., 2015; Saviola et al., 2021) suggest that GM modifications in the first years after a psychotic onset might be greatly influenced by disease severity and persistence of symptoms, as partially confirmed by the correlations observed between BPRS scores and insula GM volumes in our sample (see Supplementary Materials). Among patients with a remitting course of illness, a pattern of increase in GM volumes in selective brain regions was reported, while non-remitters presented GM reductions (Rosa et al., 2015). It is also unclear whether brain volume changes are different in those who will further develop affective or non-affective disorders (Rosa et al., 2015). Indeed, although progressive brain abnormalities may occur both in affective and non-affective psychoses, different abnormalities may be detected among the two groups, since different mechanisms may underlie the progression of these disorders (Rosa et al., 2015). Although in our sample we did not find differences in GM trajectories in affective and non-affective FEP subjects, probably due to the small sample size at follow-up, some differences were detected in both the anterior and posterior insula at baseline between non-affective FEP and chronic psychoses compared to HC, while no differences were reported for affective patients. Specifically, individuals with affective psychosis showed a significant lower GM volume in all subregions of insula when compared to HC; on the other hand, a significantly higher volume in the posterior portion is reported for non-affective patients, when compared to HC, in line with previous findings (Tian et al., 2019). Moreover, GM modifications in FEP patients observed at follow-up seem to point in the direction of a possible difference between the two groups of patients. Indeed, while GM volumes in some insular subregions of FEP patients at follow-up resembles the ones observed in SCZ patients at baseline, they still showed a statistical difference with the GM volumes of BD patients at baseline. Therefore, we can hypothesize a differential development in insula subregions in affective and non-affective psychotic disorders that could be the focus of future studies aiming at discovering the disease's trajectories.

4.3. Limitations

Our findings must be considered in light of some limitations. First, our sample size is small, even though it is in line with the numerosity of previous studies (Nelson et al., 2020; Rosa et al., 2015). Second, high rates of dropouts were observed between baseline and follow-up. Therefore, analyses based on longitudinal data need to be replicated on larger samples. Third, we acknowledge that the sample size prevented us from investigating the effects of specific variables, such as the number of episodes or hospitalizations on brain changes during the follow-up. Finally, the study had a naturalistic design, with no control over the pharmacologic and non-pharmacologic treatments.

5. Conclusions

Our findings support the heterogeneity of disease trajectories in subjects affected by psychosis, further suggesting that SCZ and other psychotic disorders cannot be regarded in terms of only deficits. In our

sample, the sub-parcellation of insular GM allowed us to detect different GM abnormalities in first-episode and chronic patients both at baseline and at follow-up, ultimately suggesting that the insula could represent a good marker of psychotic disorders. By using a transdiagnostic approach we were able to identify specific biomarkers underpinning psychiatric disorders within the psychotic spectrum, which is paramount in order to drive psychiatry towards precision medicine (Parkes et al., 2020). However, further studies on larger samples are needed to confirm these results as well as to explore the possible impact of clinical and pharmacological factors on insular GM volumes and its ability to differentiate between affective and non-affective trajectories.

Indeed, the identification of such diseases or trait related markers will greatly help a) the development of personalized strategies (Sverdlov et al., 2021), b) the improvement of prevention and early identification approaches (Andreou and Borgwardt, 2020; Ellis et al., 2020), and c) to pave the way for new drug development (Loiodice et al., 2021).

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Author contributions

P.B. designed this particular study, as well as the First and, along with. M.R. and A.L., the PICOS projects.

A.P, G.D, N.D, and G.S prepared the first version of the manuscript.

A. A. and L.F. carried out the data analysis.

F.C. carried out the manual tracing of insular volumes.

M.B, C.P, A.L, and M.R. supervised patient recruitment.

M.B., M.R., and P.B coordinated data management.

C.R., M.G.R. and A.F. were involved in patient recruitment.

All authors revised and approved the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2021.12.048.

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