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ABSTRACT

Background: Prefrontal cortex gyrification has been suggested to be altered in patients with schizophrenia and first episode psychosis. Therefore, it may represent a possible trait marker for these illnesses and an indirect evidence of a disrupted underlying connectivity. The aim of this study was to add further evidence to the existing literature on the role of prefrontal gyrification in psychosis by carrying out a study on a sizeable sample of chronic patients with schizophrenia and non-affective first-episode psychosis (FEP-NA) patients.
Methods: Seventy-two patients with schizophrenia, 51 FEP-NA patients (12 who later develop schizophrenia) and 95 healthy controls (HC) underwent magnetic resonance imaging (MRI). Cortical folding was quantified using the automated gyrification index (GI). GI values were compared among groups and related to clinical variables.
Results: Both FEP-NA and patients with schizophrenia showed a higher mean prefrontal GI compared to HC (all $p < 0.05$). Interestingly, no differences have been observed between the two patients groups as well as between FEP-NA patients who did and did not develop schizophrenia.
Conclusions: Our results suggest the presence of a shared aberrant prefrontal GI in subjects with both schizophrenia and first-episode psychosis. These findings support the hypothesis that altered GI represents a neurodevelopmental trait marker for psychosis, which may be involved in the associated neurocognitive deficits.

1. Introduction

Several studies consistently support the evidence that brain disconnectivity plays a key role in the pathophysiology of schizophrenia (Friston and Frith, 1995; Friston, 2002; Schmitt et al., 2011; White and Hilgetag, 2011), with particular regards to prefrontal cortex (PFC) (Rubinov and Bullmore, 2013; Zhou et al., 2015; Wheeler and Voineskos, 2014). In particular, the tension exerted by the viscoelastic nerve fibers is thought to influence cortical folding (Van Essen, 1997), with literature documenting that alterations in connectivity may lead to an altered cortical folding (Rakic, 1988; Konrad and Winterer, 2008; White et al., 2010).

In general, cortical folding has been considered an early neurodevelopmental process, which occur prior to birth and continuing into childhood (White et al., 2010; Garel et al., 2001). Importantly, this process is responsible for the correct development of convolution patterns and cortical organization through its association with myelination, synaptogenesis and pruning (Casey et al., 2005; White et al., 2010).

In this context, the investigation of cortical folding in schizophrenia might be of paramount importance, especially due to the neurodevelopmental origins of this disabling psychiatric illness (Owen et al., 2011). Indeed, it has been proposed that abnormal gyrification,

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which provides an index of degree and pattern of folding of brain cortex and an indirect sign of altered connectivity, represents a brain marker for schizophrenia (White and Gottesman, 2012). In this regard, the Gyrification Index (GI), which measures the ratio of the exposed cortical surface to the cerebral hull (Moorhead et al., 2006; Zilles et al., 1989), is among the most reliable methods used to quantify surface morphology.

In this perspective, it has been shown that the PFC is a core structure consistently found to be associated with schizophrenia, as reported by several functional (Zhou et al., 2015) and structural (Levitt et al., 2010; Castellani et al., 2012) neuroimaging studies. Indeed, the PFC has been found to be associated with selective deficits in specific cognitive domains, including working memory, executive functions and attention, abilities often found to be impaired in schizophrenia (Arnsten, 2011; Pratt et al., 2008; Nenadic et al., 2012; Brambilla et al., 2013a, 2013b). Additionally, in schizophrenia, PFC alterations have been also reported to be associated with positive and negative symptoms (Der-Avakian and Markou, 2012; Goghari et al., 2010; Nenadic et al., 2012; Delvecchio et al., 2017a). Therefore, the investigation of abnormal GI in this structure represents a window for deepen our knowledge on whether PFC deficits occur earlier during brain development. Nonetheless, the evidence reporting the role of prefrontal cortical folding in schizophrenia have led to contrasting results (White and Hilgetag, 2011). Indeed, although PFC hypergyria has been reported in patients suffering from schizophrenia (Falkai et al., 2007; Vogeley et al., 2001; Nenadic et al., 2015), other authors have, in contrast, reported hypogyria (Bonnici et al., 2007; Cachia et al., 2007; Kulynych et al., 1997; Mancini-Marie et al., 2015; McIntosh et al., 2009; Nesvag et al., 2014; Palaniyappan et al., 2011; Palaniyappan and Liddle, 2012; Tepest et al., 2013) or no abnormalities (Highley et al., 2003). Similarly, the same mixed picture have been reported in first-episode patients with schizophrenia (Narr et al., 2004; Janssen et al., 2014; Wiegand et al., 2005), while only one study has investigated cortical gyrification in non-affective first-episode psychosis (FEP-NA) (Palaniyappan et al., 2013), showing hypogyria in the PFC.

Therefore, our study aimed at better clarifying the role of abnormal prefrontal gyrification in psychosis by carrying out a study on a sizeable sample of patients with FEP-NA and with chronic patients with schizophrenia. Based on previous evidence, we hypothesized that patients with schizophrenia would show abnormally folded PFC compared to healthy controls (HC), although the direction of this disruption is still not well elucidated. Moreover, by extending the analyses to FEP-NA patients we are in the position to explore, and to further clarify, whether altered PFC gyrification can be considered an early distinctive marker for psychosis and, in turn, an indirect sign of a altered underlying connectivity.

2. Methods

2.1. Participants

The sample included 51 FEP-NA, 72 patients with schizophrenia, and 95 HC. All subjects gave signed informed consent. Patients with FEP-NA were recruited within the PICOS project, which has been extensively previously described by our group (Lasalvia et al., 2012). In order to be eligible for the PICOS project only psychopathological criteria were used and the over-inclusive screening methodology of the WHO ten-country study (Screening Schedule for Psychosis; Jablensky et al., 1992) was adopted. For FEP-NA patients, the inclusion criteria were: (1) presence of (a) at least one of the following symptoms: hallucinations, delusions, qualitative speech disorder, qualitative psychomotor disorder, bizarre or grossly inappropriate behavior, or (b) at least two of the following symptoms: loss of interest, initiative and drive, social withdrawal, episodic severe excitement, purposeless destructiveness, overwhelming fear, marked self-neglect; (2) first lifetime contact with any mental health service located in PICOS area during the study period resulting from symptoms listed in (1). The exclusion criteria for FEP-NA patients were: (1) prior treatment with an antipsychotics for >3 months; (2) mental disorders due to a general medical condition; (3) moderate to severe mental retardation. The formal best-estimate diagnosis was made six months after the recruitment. Among the FEP-NA patients, 12 had later develop schizophrenia and met the following diagnoses: Paranoid schizophrenia (n = 10) and Undifferentiated schizophrenia (n = 2). The remaining 39 FEP-NA patients who did not develop schizophrenia were diagnosed with: Acute transitory psychosis (n = 13), Non-organic, non-specific psychosis (n = 11), Persistent delusional psychotic syndrome (n = 7), Schizoaffective syndrome (n = 6), Acute delusional syndrome (n = 1), Acute psychosis with schizophrenic symptoms (n = 1). Patients with schizophrenia eligible for the study were selected by means of the South-Verona Psychiatric Care Register (PCR) (Tansella and Burti, 2003), a community-based mental health register, as previously reported in our publications (Delvecchio et al., 2017a, 2017b; Brambilla et al., 2013a, 2013b). They had chronic illness. Specifically, the majority of them had residual schizophrenia and were clinically stable (N = 43) whereas the others were either in the acute phase or in remission after an acute episode.

For both patients with schizophrenia and FEP-NA patients, a formal ICD-10 diagnosis was assessed by using the Item Group Checklist (IGC) of the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) (World Health Organization, 1992). Two psychiatrists independently reviewed the relevant information and formulated the ICD-10 diagnosis. In the cases the consensus was not reached, the opinion of a third psychiatrist was solicited to clarify diagnostic problems. A non-parametric Mann-Withney *U* test was performed for comparing GI values, Intra Cranial Volumes (ICVs) and age of FEP-NA who did (N = 12) and did not (N = 39) develop schizophrenia. The results showed that the merging of the two sub-groups in a unique group of FEP-NA was possible. Specifically, no differences emerged in GI and ICV ($p > 0.1$). Instead there was a significant age difference (mean age ± SD for FEP-NA who did and did not develop schizophrenia was 30.52 ± 8.75 and 40.22 ± 11.82 respectively). The potential effect of age on the variable of interest (i.e. GI) was, in any case, factored out in the following analyses as it was entered as covariate. The clinical symptomatology of all patients was evaluated using the 24 item Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). Moreover, alcohol or substance abuse was assessed with two specific item sections (sections 11 and 12) of the SCAN. All patients with schizophrenia and FEP-NA patients with other Axis I disorders, alcohol or substance abuse, history of traumatic head injury with loss of consciousness, epilepsy or other neurological or medical diseases, including hypertension and diabetes, were excluded from the study. Patients' medication was recorded and chlorpromazine equivalent dosages were calculated.

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 Axis I disorder, determined using a brief modified version of the Structured Clinical Interview for DSM-IV- Non patient version, no history of psychiatric disorder among first-degree relatives, no history of alcohol or substance misuse and no current major medical illness. The demographic and clinical details are presented in Table 1.

2.2. Magnetic resonance imaging (MRI) protocol

Magnetic resonance scans were acquired with a 1.5 T Siemens Magneton Symphony Maestro Class scanner, Syngo MR, 2002B (Siemens, Erlagen, Germany). A standard head coil was used for radio-frequency transmission and reception of the magnetic resonance signal; restraining foam pads were used to minimize head motion. First, T1-weighted images were obtained to verify each participant's head position and the image quality, with acquisition parameters repetition time (TR) 450 ms, time to echo (TE) 14 ms, flip angle 90°, field of view (FOV) 230 × 512 mm^2, 18 slices, slice thickness 5 mm, matrix size 384 × 512, number of excitations (NEX) 2. Proton density and T2-

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Table 1
Demographic and clinical characteristics of the three groups.

	FEP-NA	SCH	HC	Statistics
Number of subjects	51	72	95	
Age, mean ± SD (range) (yrs)	30.52 ± 8.75 (18.2–57.8)	40.22 ± 11.82 (18.53–62.19)	39.14 ± 11.59 (20.33–61.49)	Univariate ANOVA Main effect of group; $F(2, 215) = 13.33$, $p < 0.001$ Post-hoc comparisons HC vs FEP; $p < 0.001$* HC vs SCZ; $p = 1.0$ FEP vs SCZ; $p < 0.001$*
Male/female	21/30	26/46	48/47	HC vs FEP; $\chi^2 = 1.164$, $p = 0.281$ HC vs SCZ; $\chi^2 = 3.449$, $p = 0.063$ FEP vs SCZ; $\chi^2 = 0.324$, $p = 0.569$
Intra cranial volume (ICV) Mean ± SD (range)	1466.95 ± 133.23 (1206.99–1720.05)	1476.29 ± 163.35 (1099.25–1862.62)	1457.21 ± 140.85 (1092.20–1888.62)	Univariate ANOVA Main effect of group; $F(2, 215) = 0.35$, $p = 0.71$ Post-hoc comparisons HC vs FEP; $p = 1.0$ HC vs SCZ; $p = 1.0$ FEP vs SCZ; $p = 1.0$
Age of onset, mean ± SD (range) (yrs)	28.6 ± 7.5 (16–52)	26.31 ± 9.1 (15–58)		
Duration of illness, mean ± SD (range) (yrs)	2.02 ± 2.9 (0–18)	13.99 ± 10.7 (0,5–43)		
Medications	Atypical: 25 Typical: 11 Unmedicated: 14	Atypical: 45 Typical: 26 Unmedicated: 1		
AP lifetime, mean ± SD (range) (yrs)	1.45 ± 3.1 (0,33–18)	11.82 ± 10.3 (0–43)		
Chlorpromazine equivalents, mean ± SD (range)	11 ± 33 (0 − 200)	215 ± 165 (25–600)		
BPRS positive symptoms, mean ± SD (range)	6.2 ± 1.5 (5–12)	11.5 ± 6.2 (5–32)		
BPRS negative symptoms, mean ± SD (range)	8.6 ± 2.4 (7–18)	11.6 ± 4.6 (7–35)		
BPRS total score, mean ± SD (range)	31.3 ± 6.3 (24–50)	44.8 ± 18 (24–125)		

FEP-NA = First Episode Non Affective Psychosis; HC = healthy controls; SCH = patients with schizophrenia; AP = antipsychotics; BPRS = Brief Psychiatric Rating Scale.
* N represents the number of fatalities.

weighted images were then acquired (TR = 2500 ms, TE = 24/121 ms, flip angle 180°, FOV = 230 × 230 mm^2, 20 slices, slice thickness 5 mm, matrix size 410 × 512, NEX 2) according to an axial plane parallel to the anterior–posterior commissures to exclude focal lesions. Subsequently, a coronal 3D magnetisation prepared rapid gradient echo (MP-RAGE) sequence was acquired (TR = 2060 ms, TE = 3.9 ms, flip angle 158°, FOV = 176 × 235 mm^2, slice thickness 1.25 mm, matrix size 270 × 512, TIME 1100 ms) to obtain 144 images covering the entire brain.

2.3. Image processing

The cortical folding and tissue measures were extracted using a reliable automated GI methodology, already described elsewhere (Bonnici et al., 2007; Moorhead et al., 2006). Briefly, the automated GI tool works through several stages. First, the whole brains were preprocessed by using the image pre-processing functions from the SPM package (http://www.fil.ion.ucl.ac.uk/spm/) (Ashburner and Friston, 2000). Specifically, the T1 scans were reoriented in native space along the anterior–posterior commissure and resliced to give a voxels size of 1 mm × 1 mm × 1 mm. Then, the brain images were segmented in native space by using a specific template previously created for this cohort (Moorhead et al., 2006).

With regard to prefrontal lobe detection, the automated GI tool provides an automated parcellation procedure which detect the anterior limit of the corpus callosum and the inter-hemispheric fissure, crucial for splitting the lobes and extracting the prefrontal lobe. Moreover, in order to calculate GI the inner and outer contours of the prefrontal lobe should be calculated. Specifically, the automated GI inner contour is traced along the entire surface of the brain. Buried sulci (i.e. those that do not communicate directly with the cortical surface on that particular slice) are also included. The inner contour is measured as a continuous unbroken line. The outer contour is extracted from the brain outline and the inter-hemisphere fissure cleave in each coronal slice, as suggested by Zilles et al. (1989). The results are then exported and the prefrontal GI calculated by dividing the inner by the outer contour. Results were given for each subject, left and right hemisphere separately, for the first 30 slices of the prefrontal lobe. The GI values were obtained averaging the 30 slices. For each subject the extracted prefrontal lobes are used to recover the gray, white and cerebrospinal fluid (CSF) tissue volumes from the SPM native space segmentations. The GI trace in each scan was qualitatively reviewed (not edited) by the principal and fourth author who were blind to group membership.

2.4. Statistical analyses

Preliminary analyses were performed in order to obtain a better description of the three groups and to decide which covariates had to be entered into the main analyses. To this aim, we carried out two univariate ANOVAs with group (FEP-NA, patients with schizophrenia and HC) as fixed factor and age or ICV as dependent variables, to explore the possible differences between groups for those variables. Moreover, χ^2 tests were used to check whether the three groups differed for the proportions of males and females.

Finally, the GI values were entered as dependent variable in a 2 × 3 repeated measures ANOVA with hemisphere (left, right) as "within subject" factor and group (FEP-NA, patients with schizophrenia, HC) as "between subject" factor. Three more 2 × 2 repeated measures ANOVAs, with hemisphere (left, right) as "within subject" factor, group (FEP-NA vs HC; patients with schizophrenia vs HC; FEP-NA vs patients with schizophrenia) as "between subject" factor, were performed to clarify the main effect of group. Age was entered as covariate in all the models. Pearson's correlations examined the possible relationship between GI, gender, age, ICV and clinical measures.

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3. Results

FEP-NA, patients with schizophrenia and HC did not differ for ICV and for the proportion of males and females within each group (all $\chi^2 < 3.3$, all $p > 0.03$). Unsurprisingly, the FEP-NA patients were significantly younger than the other two groups (all $p < 0.001$) (Table 1).

3.1. GI - repeated measures ANOVA

Refer to Table 2 for the means and standard deviations of the GI, as well as for the statistical values obtained from the analyses. The 2 × 3 repeated measures ANOVA showed a main effect of the hemisphere with the left hemisphere generally having a higher GI than the right. Also the main effect of the group was significant. No significant group x hemisphere interaction was observed. The 2 × 2 repeated measures ANOVAs comparing two groups at a time highlighted a significant difference between FEP-NA and HC, as well as between patients with schizophrenia and HC, with FEP-NA and patients with schizophrenia both having a significantly higher GI than HC. Instead, no differences were found between FEP-NA and patients with schizophrenia. Coherently with the 2 × 3 overall ANOVA, the three 2 × 2 ANOVAs reported a main effect of the hemisphere and a lack of a hemisphere x group interaction.

3.2. Correlations with clinical variables

No significant correlations were observed between GI values and ICV, gender or with the other clinical variables, such as age of onset, duration of illness, lifetime treatment with antipsychotic, chlorpromazine equivalents and BPRS scores (Pearson's correlation analyses, $p > 0.05$).

4. Discussion

In this study we provided further evidence of an altered prefrontal cortical folding in schizophrenia. Additionally, alterations in GI patterns were present in non-affective patients at their first psychotic episode. In particular, both groups had higher prefrontal GI relative to HC, whereas no differences between subjects with schizophrenia and those with FEP-NA were detected.

Specifically for schizophrenia, our results are consistent with previous findings showing hypergyria within the PFC (Falkai et al., 2007; Vogeley et al., 2001; Nenadic et al., 2015). However, other studies reported hypogiria or preserved GI in the PFC of patients with schizophrenia (Bonnici et al., 2007; Cachia et al., 2007; Kulynych et al., 1997; Mancini-Marie et al., 2015; McIntosh et al., 2009; Nesvag et al., 2014; Palaniyappan and Liddle, 2012; Palaniyappan et al., 2011; Tepest et al., 2013; Highley et al., 2003). Possible explanations for these contrasting results could be related to the relative small sample size or to the presence of discrepancy between males and females within the patients or the control group. In this regard, it has been reported that gender-related differences in brain structures have been often observed in several neuropsychiatric disorders, including schizophrenia (Ruigrok et al., 2014; Delvecchio et al., 2017b). Additionally, it might be also plausible that the different methodological approaches employed by the individual studies determined these inconsistent results. Indeed, the degree of methodological heterogeneity is relatively high, with some studies using manual or automated methods or different number of slices for calculating and assessing GI. Also, although the majority of the studies measured GI with a vertex-level approach, some others measured it across the entire lobe. Indeed, as suggested by Nenadic et al. (2015), differences in resolution (higher for the vertex-level approach) could explained the abovementioned differences in GI in schizophrenia. Interestingly, it is worth mentioning that some of the studies were carried out in multi-affected families (Falkai et al., 2007; Vogeley et al., 2001) or in high risk individuals (Harris et al., 2004), and they also found increased GI in first-degree relatives of patients with schizophrenia (Falkai et al., 2007; Vogeley et al., 2001) and in individuals at high risk who subsequently develop schizophrenia (Harris et al., 2004). Therefore, these findings suggested that increased PFC gyrification might be considered a putative endophenotype of schizophrenia and a predictive vulnerability marker for this disorder. Additionally, based on the evidence suggesting that GI is a marker that seems to be independent from age (Blanton et al., 2001), it might be plausible that might index an early developmental and a quite possibly genetic anomaly in neurodevelopment, ultimately explaining its apparent association with psychosis and schizophrenia.

In general, it has been reported that altered GI in prefrontal regions in schizophrenia represents an indirect sign of disrupted underlying connectivity (White and Hilgetag, 2011), which is thought to be determined by the presence of genetic and environmental risk factors occurring during prenatal, perinatal and early adolescent periods (Harrison, 1999; Hoistad et al., 2009; White and Hilgetag, 2011).

Interestingly, similarly to chronic patients with schizophrenia, we found that FEP-NA patients showed increased PFC GI compared to HC. Additionally, it is important noticing that this result was not influenced by the presence of a small group of FEP-NA patients who later develop schizophrenia within our group of FEP-NA patients. Therefore, these findings suggest that altered PFC GI can be considered a common biological substrate characterizing psychosis independently from disease onset and/or medications. However, to our best knowledge, only one study investigated the GI in FEP-NA patients and its results are in contrast with our findings (Palaniyappan et al., 2013). Indeed, Palaniyappan et al. (2013) showed that FEP-NA patients had hypogyria in the PFC. Nonetheless, such discrepancy might be related to the different methodological approach employed in this study, which used, in contrast from our study, a vertex-wise approach across the entire cortical surface. Therefore, further studies investigating GI in FEP patients are needed in order to better clarify the role of GI in the pathophysiology of psychosis. Nonetheless, our results further support previous evidence of

Table 2
Comparison of Gyrification Index (GI) values for the three groups. Values are reported for left and right prefrontal hemispheres and specified for the first 30 prefrontal slices. Significance of the main effect for $p < 0.05$*. Significance of the comparisons between FEP-NA and HC, SCH and HC, FEP-NA and SCH for $p < 0.02$* (Bonferroni corrected).

	GI mean values			2 × 3 repeated measures ANOVA		
Right hemisphere (mean; SD)	2.22 ± 0.12			Group	Hemisphere	Group × Hemisphere Interaction
Left hemisphere (mean; SD)	2.32 ± 0.12			$F(2, 214) = 3.47$, $p = 0.03$*	$F(2, 214) = 17.63$, $p < 0.001$*	$F(2, 214) = 1.4$, $p = 0.25$
				2 × 2 repeated measures ANOVA		
	HC	FEP-NA	SCH	FEP-NA vs HC	SCH vs HC	FEP-NA vs SCH
				Main effect of group	Main effect of group	Main effect of group
Right hemisphere (mean; SD)	2.19 ± 0.11	2.24 ± 0.12	2.25 ± 0.10	$F(1, 143) = 6.13$, $p = 0.01$*	$F(1, 164) = 10.06$, $p = 0.00$*	$F(1, 120) = 0.50$, $p = 0.48$
Left hemisphere (mean; SD)	2.30 ± 0.13	2.34 ± 0.12	2.35 ± 0.11			

FEP-NA = Non-affective first-episode psychosis patients; SCH = patients with schizophrenia; HC = healthy controls. In all the 2 × 2 repeated measures ANOVAs the main effect of the hemisphere was significant (all $p < 0.02$) while the interaction group × hemisphere was not significant (all $p > 0.5$). The main effect of Hemisphere and the Group × Hemisphere interaction of the 2 × 2 repeated measures ANOVAs mirrored the findings of the main 2 × 3 repeated measures ANOVA, with all the models giving significant differences between the Hemispheres regardless the Group [FEP-NA vs HC - Hemisphere $F(1, 143) = 24.15$, $p < 0.001$, Group × Hemisphere $F(1, 143) = 0.03$, $p = 0.87$; SCH vs HC - Hemisphere $F(1, 164) = 29.36$, $p < 0.001$, Group × Hemisphere $F(1, 164) = 0.80$ $p = 0.37$; FEP-NA vs SCH - Hemisphere $F(1, 120) = 8.59$, $p = 0.004$, Group × Hemisphere $F(1, 120) = 1.47$, $p = 0.23$].

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disrupted PFC connectivity in FEP. Specifically, Satterthwaite et al. (2016) showed altered frontal cortex in youth with psychosis spectrum disorders. Moreover, similarly to schizophrenia, altered structural (Luck et al., 2011; Price et al., 2008) and functional (Alonso-Solís et al., 2012; Argyelan et al., 2015; Fornito et al., 2013; Schmidt et al., 2013) PFC connectivity has also been reported for FEP. Therefore, despite the presence of inconsistencies in the available literature, our study suggests that altered GI and, consequently, disrupted PFC connectivity represents an indirect developmental marker for psychosis, overcoming the categorical diagnosis of schizophrenia (White and Gottesman, 2012), in line with a dimensional approach as per the Research Domain Criteria approach (Cuthbert and Insel, 2010).

Furthermore, our results also showed the presence of brain asymmetry in all our groups, with left PFC having higher GI values compared to right PFC. Specifically for HC, our findings are in line with previous literature, reporting functional and structural asymmetries of brain hemispheres in this group of individuals (Chen and Omiya, 2014; Toga and Thompson, 2003). Interestingly, some studies also reported that HC had a left > right pattern of PFC gyrification (Palaniyappan et al., 2011; Vogeley et al., 2000; Wiegand et al., 2005; Wiegand et al., 2005; Narr et al., 2004). Therefore, our results further confirmed that brain asymmetry is an evolutionally adaptive phenomenon occurring in the human brain, which is associated with normal brain functional/cognitive lateralization.

Similarly, we also observed the presence of the same gyrification asymmetry in both FEP-NA and chronic schizophrenia. Interestingly, this result seems to be in contrast with many functional and structural MRI studies in schizophrenia, which reported the lack of normal hemisphere asymmetry in this disabling disorder (Ribolsi et al., 2014; Sun et al., 2017). This lack of normal hemisphere asymmetry is thought to represent a derailment in the process determining the normal hemispheric specialization, possibly reflecting an altered abnormal underlying brain connectivity (Oertel-Knöchel and Linden, 2011; Ribolsi et al., 2014; Mitchell and Crow, 2005). Nevertheless, a similar general consensus on the abnormalities in gyrification asymmetry in this patients group has not been reached yet. Indeed, findings suggested either a lack or a reversed pattern of normal gyrification asimmetry in schizophrenia (Wiegand et al., 2005; Narr et al., 2004; McIntosh et al., 2009; Mancini-Marie et al., 2015; Palaniyappan et al., 2011). Therefore, given the general heterogeneity in GI literature, more research will be useful for clarifying the role of PFC gyrification asymmetry in psychosis. Finally, in our study, no GI differences between individuals with schizophrenia and FEP-NA patients have been observed and no associations were found between GI and clinical symptoms. Therefore, this result supports the hypothesis that altered cortical folding is a common biological trait marker characterizing psychoses, regardless of chronicity, medication, and illness severity.

5. Limitations

This study should be considered in light of few limitations. First, sample size was relatively small (although in line, or even higher than studies published so far). Second, patients with schizophrenia were chronically ill and treated, therefore we cannot fully rule out the possible role of chronicity and antipsychotic medication in GI alterations. However, no significant correlations were observed between GI and clinical variables, including length of illness and duration and doses of antipsychotic treatment. Finally, data on duration of untreated psychosis (DUP) were not available for this study. In general, this clinical measure was poorly investigated in association with GI in psychosis. Indeed, to the best of our knowledge, only one study, which did not show any significant results, explored the association between DUP and GI in schizophrenia (Schultz et al., 2010). This negative result is not surprising especially because previous evidence reported that GI is determined early in brain development (Zilles et al., 1989) further sustaining that DUP, and clinical symptoms in general, should have no significant effects on GI patterns.

6. Conclusions

In conclusion, our findings add further evidence to the existing literature by showing the presence of a shared aberrant prefrontal GI in schizophrenia and FEP-NA, thus suggesting that altered GI may represent a trait marker for psychosis. From this perspective, GI alteration could be a putative biomarker of psychosis helping for an early detection of individuals prone to develop psychosis. Nonetheless, future longitudinal studies coupled with cognitive investigations are expected to further explore GI in large samples of subjects at risk to develop psychosis followed over time before and after treatment.

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Contributors

RZ, GC, CB, GD and PB prepared the first versions of the manuscript.
PB and SL designed the study.
RZ, CB and PB carried out the data analysis.
RZ, AM, SL and PB implemented the imaging techniques.
Matteo B, Marcella B, and MR coordinated data management and supervised patient recruitment.
CP, VM, MGR were involved in patient recruitment.
AL, MR and PB designed the PICOS project.
FS and RC acquired imaging data.
All authors revised and approved the final versions of the manuscript.

Conflict of interest

The authors report no financial interests or potential conflicts of interest.

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