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ORIGINAL ARTICLE

Insular pathology in young people with high-functioning autism and first-episode psychosis

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Background. Autism Spectrum Disorders (ASD) and psychosis share deficits in social cognition. The insular region has been associated with awareness of self and reality, which may be basic for proper social interactions.

Methods. Total and regional insular volume and thickness measurements were obtained from a sample of 30 children and adolescents with ASD, 29 with early onset first-episode psychosis (FEP), and 26 healthy controls (HC). Total, regional, and voxel-level volume and thickness measurements were compared between groups (with correction for multiple comparisons), and the relationship between these measurements and symptom severity was explored.

Results. Compared with HC, a shared volume deficit was observed for the right (but not the left) anterior insula (ASD: $p = 0.007$, FEP: $p = 0.032$), and for the bilateral posterior insula: (left, ASD: $p = 0.011$, FEP: $p = 0.033$; right, ASD: $p = 0.004$, FEP: $p = 0.028$). A voxel-based morphometry (VBM) conjunction analysis showed that ASD and FEP patients shared a gray matter volume and thickness deficit in the left posterior insula. Within patients, right anterior ($r = -0.28$, $p = 0.041$) and left posterior ($r = -0.29$, $p = 0.030$) insular volumes negatively correlated with the severity of insight deficits, and left posterior insular volume negatively correlated with the severity of 'autistic-like' symptoms ($r = -0.30$, $p = 0.028$).

Conclusions. The shared reduced volume and thickness in the anterior and posterior regions of the insula in ASD and FEP provides the first tentative evidence that these conditions share structural pathology that may be linked to shared symptomatology.

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Key words: Autism spectrum disorders, first-episode psychosis, insula, morphology, cortical thickness, volume.

Introduction

Autism spectrum disorders (ASD) and psychotic disorders are complex psychiatric disorders of neurodevelopmental origin that share clinical and cognitive symptomatology (Rapoport *et al.* 2009; Hommer & Swedo, 2015). Both patient groups present difficulties in social cognition, in integrating information from the external and internal world, and in the perception/understanding of self (self-awareness) and others, resulting in a limited ability to interpret (or understand) reality and themselves, and to generate appropriate responses to external demands (Couture *et al.* 2010; Rapoport *et al.* 2009; Modinos *et al.* 2011). It is unclear whether these shared clinical/cognitive phenotypes are related to a common neuroanatomical substrate but recent evidence suggests the insular cortex is a key region for these cognitive functions (Craig, 2009; Nieuwenhuys, 2012; Moran *et al.* 2014).

The insula is a highly interconnected multimodal cortical region. While the posterior insula receives interoceptive and external somatosensory perception

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input, the anterior insula integrates these with cognitive and emotional responses to the same stimuli, which are received via its connections with the anterior cingulate and prefrontal cortices and the amygdala (Penfield & Faulk, 1955; Craig, 2009; Craig, 2011). Therefore, both the anterior and posterior insular cortex may play a key role in self-awareness, attribution of mental and emotional states to oneself and others (theory of mind), and distinction between self-/non-self, basic for adequate interpersonal relations and for interpreting and understanding oneself and reality. Insular dysfunction has therefore been proposed as a neural substrate for deficits involving these basic, specific human abilities (Lombardo *et al.* 2010; Cabanis *et al.* 2013; Fett *et al.* 2015) and in the pathophysiology of psychosis. Furthermore, a recent meta-analysis of voxel-based morphometry (VBM) studies showed that a reduction of largely anterior insular volume is associated with different psychotic and non-psychotic psychiatric diagnoses (Goodkind *et al.* 2015). This meta-analysis did not include ASD, in which social cognition difficulties are not only core but defining. In this study, we evaluated whether children and adolescents with either ASD (and no mental retardation) or FEP showed insular volume and thickness abnormalities (globally, and in the anterior and posterior subregions) compared with healthy controls, and whether both patient groups had spatially overlapping insular volume/thickness deficits at the subregional level. We hypothesized that both patient groups would show insular deficits and we explored if these deficits would be associated with severity of symptoms (socio-communication deficits, insight deficits).

Methods and Materials

Participants

Thirty children and adolescents with ASD and no mental retardation per DSM-IV-TR criteria, 29 with FEP, and 26 healthy controls, matched for age, handedness and socioeconomic status (SES), were recruited for this study. The study was developed in the Child and Adolescent Psychiatry Department at Hospital Gregorio Marañón, Madrid, Spain. ASD patients were recruited through family associations and the outpatient clinic, and FEP patients were recruited at the inpatient or outpatient clinic at their first episode of psychosis. Healthy controls were recruited from the community, at publicly-funded schools in the same geographic area as patients.

The inclusion criteria for all patients were being 7–18 years of age at the first assessment, speaking Spanish correctly, and having a DSM-IV-TR diagnosis of either a first episode of psychosis or pervasive developmental disorder (PDD). The inclusion criteria for healthy controls were the same as for patients, except for no current or previous psychiatric disorder. Exclusion criteria for all groups included mental retardation per DSM-IV-TR criteria, neurological disorders, history of head trauma with loss of consciousness, and pregnancy. Fulfilling diagnostic criteria for any psychiatric diagnosis other than the main diagnosis in each group (FEP or ASD) was also an exclusion criterion.

The study protocol and informed consent form were approved by the Institutional Review Board of Hospital Gregorio Marañón in Madrid. All parents or legal guardians gave written informed consent after receiving complete information about the study, and patients and controls agreed to participate.

Diagnostic assessment

All diagnostic assessments were conducted by child and adolescent psychiatrists with extensive experience in diagnosing ASD and psychosis, after directly assessing the patient and family and reviewing all available medical and educational reports. The Spanish adaptation of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman *et al.* 1997) was administered to both patient groups and healthy controls at the first visit, to obtain diagnoses in FEP patients and rule out concomitant psychiatric disorders in all groups. It was administered individually to parents and children/adolescents in separate interviews. Patients were included in the ASD group if they fulfilled DSM-IV-TR criteria for PDD after direct observation and taking a full psychiatric and developmental history from at least one informant, typically the mother. The Autism Diagnostic Observation Schedule-Generic (ADOS-G) (Lord *et al.* 2000) was administered by experienced ADOS-research trained child psychiatrists when the diagnosis was not clear (5 cases). The final diagnosis was based on best clinical judgment considering all the available information, (Volkmar *et al.* 2014), by board-certified child psychiatrists clinically certified to administer the ADI and research-certified to administer the ADOS. Patients were included in the FEP group if they fulfilled any DSM-IV-TR diagnosis of psychotic disorder (other than drug-induced psychosis) after assessment.

Clinical and cognitive assessment

For all groups, SES was estimated from parental years of education. Handedness was assessed with item 5 of the Neurological Evaluation Scale (NES) (Buchanan & Heinrichs, 1989). An estimated intelligence quotient (IQ) was calculated in FEP and control group subjects

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using the vocabulary and block-design tests of the Wechsler Intelligence Scale for Children (WISC-R) in subjects under 16 years of age, or the Wechsler Adult Intelligence Scale (WAIS-III) in subjects 16 years of age or older (Wechsler, 2003). A full IQ was obtained in the ASD group (Merchan-Naranjo *et al.* 2012).

The Positive and Negative Syndrome Scale (PANSS) (Peralta & Cuesta, 1994) was administered to both patient groups (intraclass correlation coefficients for PANSS inter-rater reliability were above 0.8). PANSS positive, negative, general, and total subscores were computed. Following Kastner *et al.* (2015) (Kastner *et al.* 2015) specific items of the PANSS were used and summed to create a '*difficulties in social interaction*' score [items N1 ('blunted affect'); N3 ('poor rapport'), and N4 ('social withdrawal')], a '*difficulties in communication*' score [(items N5 ('difficulties in abstract thinking') and N6 ('lack of spontaneity and flow of conversation')], and a '*stereotypies/narrowed interests*' score [items G5 ('mannerism'), G15 ('preoccupation'), and N7 ('stereotyped thinking')]. The three scores were summed to compute a total dimensional autism severity score (PAUSS). The PAUSS has been validated in adult-ASD and disease-control samples (Kastner *et al.* 2015). Finally, insight was assessed with PANSS item G12. In all PANSS and PAUSS items and scores, higher scores mean greater severity of symptoms.

The Clinical Global Impression-Severity scale (CGI-S) (Guy, 1976) was also administered to both patient groups. Psychosocial functioning was assessed in all patients and healthy controls with the Children's Global Assessment of functioning Scale (CGAS) (Endicott *et al.* 1976). For both patient groups, cumulative antipsychotic dose at baseline (converted to chlorpromazine equivalent doses) (Rijcken *et al.* 2003; Andreasen *et al.* 2010) were computed.

Image acquisition and analyses

Image acquisition

All participants were scanned using the same Philips Intera 1.5T MRI scanner (Philips Medical Systems, Best, The Netherlands). Two magnetic resonance sequences were acquired for all participants: a high-resolution three-dimensional T1-weighted sequence with 1-mm slice thickness [echo time (TE) = 9.2 ms, repetition time (TR) = 25 ms, field of view (FOV) = 256 mm, and in-plane voxel size 0.98 mm^2], and a T2-weighted turbo spin echo sequence with 3-mm slice thickness (TE = 120 ms, TR = 5809 ms, FOV = 256 mm, and in-plane voxel size 1 mm^2). Both T1- and T2-weighted images were used for clinical neurodiagnostic evaluation by an independent neuroradiologist. No participants showed clinically significant brain pathology.

Measurement of insular volume and thickness

Image quality was determined visually and with the 'Check sample homogeneity' tool in the SPM VBM8 toolbox (v.r435, http://dbm.neuro.uni-jena.de/vbm/check-sample-homogeneity/). Insular volume and thickness were estimated using the open-source Advanced Normalization Tools (ANTs) package. ANTs are optimally suited for a combined region-of-interest and VBM approach. ANTs performance is comparable with FreeSurfer (Tustison *et al.* 2014), and we found a high correlation between ANTs and FreeSurfer output (see online Supplemental Fig. S1). The image preprocessing steps to create gray matter (GM) and cortical thickness maps in native and normalized space are detailed in Tustison *et al.* (2014). Furthermore, the bilateral anterior and posterior insular regions were segmented in a study-specific template using the multi-atlas label fusion algorithm (Wang & Yushkevich, 2013) and expert-based manual segmentations (Klein & Tourville, 2012) (see online Supplemental Fig. S2). Insular regions were transformed from the template onto the T1 images of each participant and regional insular volumes and thickness were extracted. The normalized cortical GM volume and thickness maps were fed into a VBM analysis (see Statistics) after smoothing with a Gaussian kernel of four sigma.

Statistical analyses

Group-wise analysis of demographic and clinical characteristics

Differences in demographic and clinical variables between diagnostic groups were assessed using parametric or non-parametric tests with quantitative or categorical variables, as appropriate.

Group-wise analysis of insular volume

To test whether regional insular volume and thickness were associated with FEP and ASD, we used the general linear model (after checking for general linear model assumptions) with diagnostic group (ASD, FEP, control group) as the independent variable. *Post hoc* comparisons with Bonferroni correction were also conducted to explore the effect of diagnosis at a pairwise level. Effect size is given as Cohen's *d*.

VBM conjunction analysis

In order to assess whether there were subregional areas where both patient groups had insular volume or thickness deficits, a VBM conjunction analysis was conducted using as a mask those insular regions that had previously shown a significant diagnostic effect. Our conjunction analysis consisted of using the

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minimum statistics under the conjunction null hypothesis (Nichols *et al.* 2005) and computing the intersection of the thresholded statistical maps in order to delineate consistent insular GM deficits in the patient groups. The conjunction null hypothesis tests whether all effects are different from null rather than whether the combined effect is null (global null hypothesis).

VBM conjunction results were produced from permutation-based (5000) non-parametric testing (Winkler *et al.* 2014) and threshold-free cluster enhancement [TFCE; (Smith & Nichols, 2009)]. All statistical results were thresholded at $p < 0.05$, family-wise error corrected for multiple comparisons. TFCE was used to avoid choosing an arbitrary cluster-forming threshold.

Age, sex, and total brain volume were included as covariates both in pair-wise and VBM conjunction analyses, as they are known to be related to structural brain measures. IQ was not included in the analyses because of a lack of significant association with total or regional insular volume and thickness (online Supplemental Fig. 3). Given the number of individuals with zero antipsychotic usage, we explored the relationship of cumulative antipsychotic dose (box-cox transformation computed as it showed a largely skewed distribution) with total or regional insular morphometric measurements only in the 'antipsychotic user' group (n FEP = 27, ASD = 8). A Pearson correlation was computed between the unstandardized volume and thickness residuals (by regressing out age, sex, total brain volume, and diagnosis) and the transformed cumulative dose data in this group, finding no significant association. Therefore, cumulative antipsychotic dose was not included in the analyses as a covariate.

Association between demographic, clinical variables, and insular volume and thickness measurements

The associations between insular volume/thickness for ASD/FEP/combined patient group and symptom severity were explored using Pearson correlation coefficients. The correlations between regions showing insular reductions and the severity of 'autistic' symptoms (using PAUSS social and total scores), insight deficits (using item PANSS G12) and psychotic symptoms (using PANSS positive, general, and total scores) were examined. No multiple comparison correction was done due to the exploratory nature of these analyses.

Results

Group-wise analysis of demographic and clinical characteristics

Demographic and clinical characteristics of the study sample are presented in Table 1. The three groups did not differ in age, handedness, or SES. The FEP group had a higher proportion of females than the ASD or control group. The FEP and ASD groups had lower estimated and global IQ, respectively, relative to healthy controls. Severity of positive, negative, and general psychotic symptoms and severity of global disease (CGI) were greater in the FEP than the ASD group. No differences between patient groups were found in severity of insight deficits or autistic-related traits (PAUSS total scores and subscores). Relative to the ASD sample, FEP patients had higher antipsychotic prescription rates (23% *v.* 93%, respectively), and cumulative antipsychotic dose at baseline was higher in the FEP group ($p < 0.001$).

Group comparisons of overall and subregional insular volume and thickness

See Fig. 1. For insular volume, there was an effect of diagnosis for the right but not the left anterior insula [left: $F(1,79) = 1.53$, $p = 0.224$, $d = 0.39$, right: $F(1,79) = 5.70$, $p = 0.005$, $d = 0.76$)]. The effect in the right anterior insula was present in both patient groups compared with the healthy control group (ASD: $p = 0.007$, FEP: $p = 0.032$). For the posterior insula, there was a bilateral effect of diagnosis [left: $F(1,79) = 5.29$, $p = 0.007$, $d = 0.73$, right: $F(1,79) = 6.21$, $p = 0.003$, $d = 0.79$] caused by a shared deficit in ASD and FEP compared with the healthy control group (left insula, ASD: $p = 0.011$, FEP: $p = 0.033$; right insula, ASD: $p = 0.004$, FEP: $p = 0.028$). ASD and FEP groups did not differ significantly from each other.

For insular thickness, there was a trend toward effect of diagnosis in the left posterior insula [$F(1,79) = 2.92$, $p = 0.059$, $d = 0.54$] which, without Bonferroni correction, was explained by a shared deficit in ASD and FEP relative to healthy controls (ASD: $p = 0.044$, FEP = 0.035). After Bonferroni correction, this was no longer significant. No other significant effects of diagnosis were found.

Subregional shared deficits

Using TFCE, after correction for multiple comparisons, the conservative minimum statistic conjunction across ASD and FEP revealed one cluster with significant GM volume deficit (size: 31 voxels) and one cluster with thickness deficit (size: 335 voxels) in the left posterior insula. The volume and thickness for the two clusters were extracted and plotted against diagnosis (see Fig. 2 and Table 2). There were no subregional differences in insular volume between the patient groups.

Associations between ASD/FEP insular deficits and clinical symptoms

Within the combined ASD/FEP sample, there were significant negative correlations between severity of insight deficits (PANSS item G12) and right anterior

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Table 1. *Sociodemographic and clinical characteristics of the sample*

Continuous variables	ASD ($n = 30$) M	ASD ($n = 30$) S.D.	FEP ($n = 29$) M	FEP ($n = 29$) S.D.	CONTROL ($n = 26$) M	CONTROL ($n = 26$) S.D.	Statistic	Sig.
Age. *Years Mean* (S.D.)	13.3	1.99	14.1	0.98	13.1	2.43	[a]$F_{82;2} = 2.27$	0.11
Parental years of education. *Mean* (S.D.)	14.2	3.09	13.3	4.17	14.0	3.39	[a]$F_{80;2} = 0.53$	0.59
IQ. *Total score Mean* (S.D.)	88.0	18.1	87.0	25.6	112.6	15.3	**[a]$F_{77;2} = 11.82$**	**<0.001****
Psychotic symptoms. *Score Mean* (S.D.)								
PANSS. *Positive*	11.1	4.4	22.5	7.0	–		**[b]$T_{47.7} = -7.31$**	**<0.001**
PANSS. *Negative*	19.6	6.1	21.4	8.8			**[b]$T_{49.9} = -0.88$**	0.39
PANSS. *General*	34.8	8.7	43.0	13.4			**[b]$T_{53} = -2.74$**	**<0.01**
PANSS. *Total*	65.3	15.9	87.7	27.6			**[b]$T_{45.6} = -3.71$**	**<0.001**
Autistic-related symptoms. *Score Mean* (S.D.)								
PAUSS. *Social Interaction*	8.15	2.75	9.14	4.21			[b]$T_{48.7} = -1.04$	0.31
PAUSS. *Communication*	6.25	1.98	6.59	2.63	–		[b]$T_{51} = -0.52$	0.61
PAUSS. *Stereotypies/narrowed interests*	7.69	2.72	7.21	2.86			[b]$T_{53} = 0.64$	0.52
PAUSS. *Total*	21.8	6.6	22.9	8.9			[b]$T_{51} = -0.49$	0.62
Insight								
PANSS Item G12. *Mean* (S.D.)	3.62	1.3	3.62	1.6	–		**[b]$T_{53} = -0.01$**	0.99
Illness severity/functioning								
CGI-S. *Score Mean* (S.D.)	4.03	0.87	4.86	1.08	–		**[b]$T_{55} = -3.18$**	**0.01**
CGAS. Score *Mean* (S.D.)	48.1	12.2	47.2	15.9	92.6	5.6	**[a]$F_{76;2} = 103.7$**	**<0.001****
Antipsychotic cumulative dose. Chlorpromazine equivalents (*Milligrams*) *Median [range]*	0 [0–682]		2648.6 [0–89.875]				**[c]$Z = -3.04$**	**<0.001**

Categorical variables	**ASD ($n = 30$)**		**FEP ($n = 29$)**		**CONTROL ($n = 26$)**		**Statistic**	**Sig.**
Sex. *Male – N* (%)	28	93.3	18	62.1	25	96.2	**[d]$\chi^2_{85} = 13.07$**	**<0.01***
Handedness. *N* (%)								
Right-handed	25	86.2	24	92.3	21	87.5		
Left-handed	3	10.3	2	7.7	1	4.2	[d]$\chi^2_{79} = 2.76$	0.67
Ambidextrous	1	3.4	0	0	2	8.3		
Antipsychotic treatment. *N* (%)	8	26.6	27	93.0			**[c]$\chi^2_{59} = 54.9$**	**<0.001**
FGA, *N* (%)	0	0	1	3.4				
Combination SGA + FGA, *N* (%)	1	3.3	1	3.4	–		[d]$\chi^2_{59} = 1.69$	0.64
SGA, *N* (%)	7	23.3	25	86.2			**[d]$\chi^2_{59} = 51.1$**	**<0.01**

Significant differences ($p < 0.05$) in bold. ASD, Autism Spectrum Disorders; CGAS, Children's Global Assessment Scale; CGI-S, Clinical Global Impression – Severity scale; FEP, First Episode of Psychosis; FGA, First Generation Antipsychotics; IQ, Intellectual Quotient (estimated for FEP and control group, full scale IQ for ASD, see Methods section); PANSS, Positive and Negative Syndrome Scale; PAUSS, PANSS autism severity score; SGA, Second-Generation Antipsychotics. a ANOVA; b *t*-test; c Mann–Whitney *U* test; d Chi-square test.

*CONTROL *v.* FEP ($\chi^2 = 14.18$; $p < 0.01$); ASD *v.* CONTROL ($\chi^2 = 0.22$; $p = 0.64$); ASD *v.* FEP ($\chi^2 = 8.39$; $p < 0.01$) **CONTROL *v.* FEP ($p < 0.01$); ASD *v.* CONTROL ($p < 0.01$); ASD *v.* FEP ($p = 0.98$) ***CONTROL *v.* FEP ($p < 0.01$); ASD *v.* CONTROL ($p < 0.01$); ASD *v.* FEP ($p = 0.97$).

insular volume ($r = -0.28$, $p = 0.041$) and left posterior insular volume ($r = -0.29$, $p = 0.030$) (Fig. 3). Illness severity (CGI-S score) negatively correlated with left posterior insular volume ($r = -0.29$, $p = 0.027$) and PAUSS total score negatively correlated with VBM conjunction cluster volume ($r = -0.30$, $p = 0.028$). There were no other significant correlations.

Discussion

A direct comparison of a well-characterized sample of young patients with high-functioning ASD or FEP and healthy controls revealed that (i) both patient groups showed GM volume reductions in the right anterior and left and right posterior insular cortex compared

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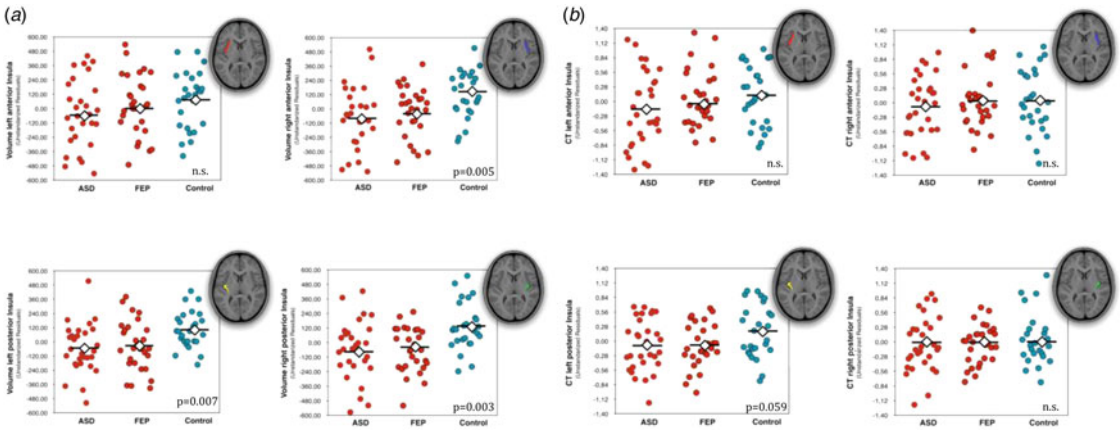

Fig. 1. Differences between diagnostic groups in subregional insular volume and thickness measurements. (*a*) Unstandardized residuals for left/right anterior and posterior insular volumes after controlling for age, sex and total brain volume for both patient groups (red dots) and the control group (blue dots); (*b*) Unstandardized residuals for left/right anterior and posterior insular thickness after controlling for age, sex, and total brain volume for both patient groups (red dots) and the control group (blue dots). ASD, autism spectrum disorders; CT, cortical thickness; FEP, first-episode psychosis.

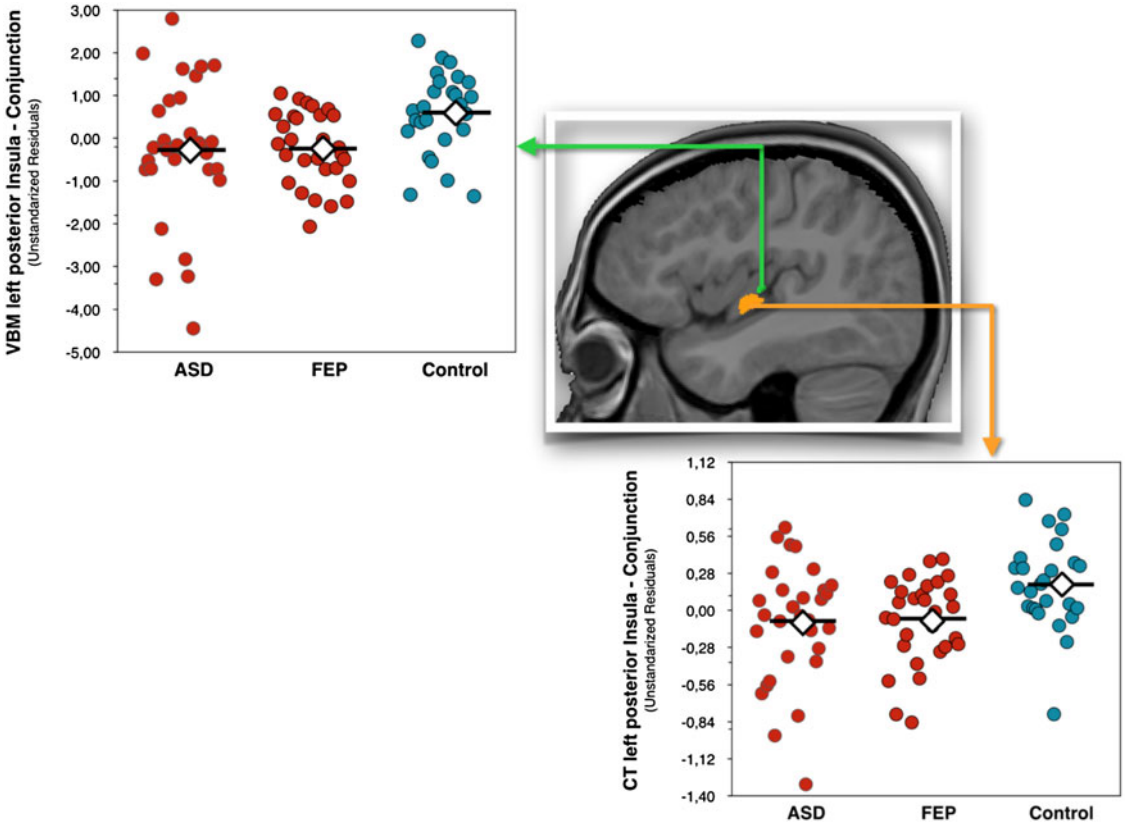

Fig. 2. Clusters of shared insular volume/thickness deficits for the ASD and FEP sample relative to healthy controls. VBM conjunction analysis across ASD and FEP revealed one shared cluster with significant GM volume deficit (size: 31 voxels) and one cluster with thickness deficit (size: 335 voxels) in the left posterior insula. The volume and thickness for the two clusters are plotted against diagnosis (ASD and FEP – red dots, and controls – blue dots). ASD, autism spectrum disorders; CT, cortical thickness; FEP, first-episode psychosis.

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Table 2. *Clusters of shared insular volume/thickness deficits for the ASD and FEP sample relative to healthy controls (VBM conjunction analysis)*

Measurement	Diagnosis	Size (voxels)	lowest *p*	X	Y	Z	Structure
Volume							
	ASD	31	0.0098	−40	−11	1	Posterior Insula
	FEP	31	0.045	−40	−13	5	Posterior Insula
Thickness							
	ASD	335	0.012	−42	−5	−7	Posterior Insula
	FEP	335	0.027	−41	−10	−5	Posterior Insula

ASD, Autism Spectrum Disorders; FEP, First Episode of Psychosis.

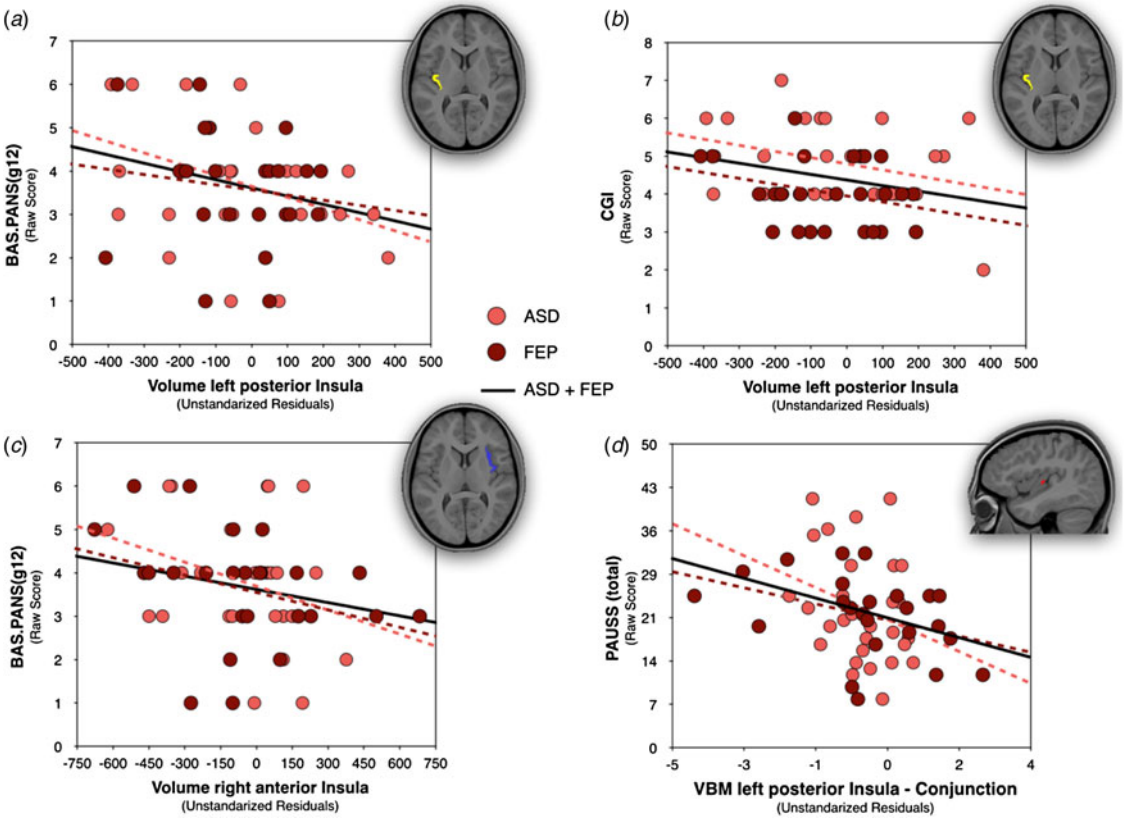

Fig. 3. Significant associations between ASD/FEP insular volume deficits and clinical symptoms. ASD, Autism Spectrum Disorders; CGI-S, Clinical Global Impression – Severity scale; FEP, First Episode of Psychosis; PANSS, Positive and Negative Syndrome Scale; PAUSS, PANSS autism severity score. (*a*) Correlation between Left posterior insula volume and insight (G12 item from the PANSS). (*b*) Correlation between left posterior insula volume and Clinical Global Impression score. (*c*) Correlation between Right anterior insula volume and insight (G12 item from the PANSS). (*d*) Correlation between Left posterior insula conjunction cluster and autism severity score from the PAUSS.

with controls; (ii) patient groups had a spatially overlapping subregional volume and thickness deficit in the left posterior insula; and (iii) in the combined patient group, regional insular volume deficits were associated with severity of symptoms (socio-communication and insight deficits). We did not find any distinct specific insular deficit for ASD or FEP patients.

The only VBM study we know of, directly comparing ASD and patients with psychosis, reported a non-significant lower insular GM volume in adolescents and adults with ASD relative to healthy controls and

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no abnormalities in individuals with chronic schizophrenia and therefore long exposure to antipsychotics (Radeloff *et al.* 2014). This is, to the best of our knowledge, the first study to assess the overlap of insular volume and thickness deficits in young people with ASD or FEP. Our results support the hypothesis that insular structural deficits are common in ASD and FEP. This fits within a broader context of the insula as a crucial region for subserving social processing-related skills (perception and understanding of self and others, known to be affected in both neurodevelopmental conditions) and its involvement in reality distortion and emergence of positive psychotic symptoms (Lombardo *et al.* 2010; Palaniyappan & Liddle, 2012; Cabanis *et al.* 2013).

Our results are consistent with those from studies reporting an insular deficit separately for both disorders (Kosaka *et al.* 2010; Riva *et al.* 2011; Moran *et al.* 2014) or jointly using meta-analytic approaches (Ellison-Wright *et al.* 2008; Kosaka *et al.* 2010; Rais *et al.* 2012; Shepherd *et al.* 2012; Moran *et al.* 2014). The findings are also congruent with results from original and meta-analytic fMRI studies showing abnormal activation and/or connectivity of this structure within the 'social brain' network in both patient groups (Pinkham *et al.* 2008; Di Martino *et al.* 2009).

With regard to insular regions, we found that volume deficits in the right anterior insula were present both in ASD and FEP, in keeping with findings of structural and functional connectivity deficits in this subregion in ASD patients (Kosaka *et al.* 2010; Ebisch *et al.* 2011), in psychosis patients (Makris *et al.* 2006; Shepherd *et al.* 2012), and even in neurotypical adults with higher autistic trait load (Di Martino *et al.* 2009). The anterior insular cortex has been related to a number of higher-order processes such as time-, bodily-, and self-awareness, as well as to evaluative, experiential, outcome uncertainty and expressive aspects of individual emotions, and particularly in respect to social and other interpersonal phenomena (shared or empathy-related pain). The deviance of these integration functions may be clinically reflected in difficulties differentiating internal- from external-generated information. This would be congruent with fact that anterior insular deficits in our sample significantly correlated with severity of insight deficits (related to the capacity of awareness).

Although original studies and meta-analyses have reported reductions of insular volume mainly affecting or largest in the anterior part (Makris *et al.* 2006; Takahashi *et al.* 2009; Shepherd *et al.* 2012; Goodkind *et al.* 2015), the posterior insular cortex is also reportedly affected both in ASD and psychosis patients, both at a structural (Kosaka *et al.* 2010; Shepherd *et al.* 2012) and functional level (Anderson *et al.* 2010, Ebisch *et al.* 2011). Posterior insular cortex deficits have also been shown in pathologies that involve anosognosia (e.g. hemiplegia) (Klein *et al.* 2013), which could be related to diseases with evident insight deficits, such as ASD and psychosis. Indeed, our patient sample showed similar severity of insight deficits, associated with the posterior insular volume deficit.

Diagnostic categories in psychiatry may not capture fundamental underlying mechanisms of dysfunction (Insel *et al.* 2010). It therefore makes sense to study whether complex psychiatric disorders of neurodevelopmental origin with common clinical/cognitive deficits in behavioral domains, such as those that are part of the Research Domain Criteria (RDoC) matrix (http://www.nimh.nih.gov/research-priorities/rdoc), have common underlying biological features.

In the combined ASD/FEP sample, we found that reduced posterior insular volume was associated with severity of autistic-like symptoms (a combination of items related to social and communication deficits extracted mainly from the PANSS negative subscale) and right anterior insula with insight deficits. In psychosis patients, insular structural deficits have been associated with presence and severity of positive symptoms and severity of negative symptoms (Takahashi *et al.* 2009; Moran *et al.* 2014) and an abnormal activation of this region during self-referential processing tasks has been reported in clinical and subclinical forms of psychosis (Modinos *et al.* 2011). In our sample, we did not find an association between positive or negative psychotic symptoms and insular deficits in the combined ASD/FEP sample, but the sample size was limited and the analysis was exploratory in nature, so these findings warrant replication.

We cannot tell from our data if insular abnormalities are specific only to ASD and FEP or are a common nonspecific feature of human mental illness, as others have proposed (Craig, 2009), and some have shown in different severe psychiatric disorders (Goodkind *et al.* 2015). These findings, together with those from our study, support the idea that a transdiagnostic approach is key to capturing fundamental underlying mechanisms of brain dysfunction, an approach that is central in emerging initiatives such as the RDoC project (Insel *et al.* 2010). Further studies combining different psychiatric conditions are needed in order to understand the specificities of insular pathology.

The strengths of this study include: (i) the inclusion of two groups of traditionally separated psychiatric conditions: ASD and psychosis; (ii) psychosis patients were young people with first-episode psychosis, reducing the limitations inherent to the effect of chronicity and long-term psychopharmacological treatment; (iii) the groups were balanced in terms of age, intellectual ability, handedness, and SES; (iv) the study is in line

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with the NIMH RDoC initiative, which asks investigators to step back from classic symptom-based diagnostic categories and focus on studying common endophenotypes and/or clinical/cognitive domains across diagnoses (e.g. reality distortion, social-communication deficits, or lack of insight).

Our study should be interpreted in light of a number of limitations. Since ASD and FEP samples were hard to acquire, the sample size of this study was limited, which may have led to type II errors. Furthermore, the correlations between clinical variables and volume measurements should be interpreted with caution as we did not apply any formal multiple-testing correction in these analyses. These analyses were exploratory in nature, and therefore it was not clear if correction for multiple comparisons was appropriate (Perneger, 1998). Although cumulative antipsychotic dose did not correlate with insular volume or thickness in the 'medicated' subsample, the analyses in this regard are limited due to sample size and differential distribution of medication intake between diagnostic groups (greater in the FEP group). Finally, the relationship between structural findings and brain function is far from clear. The causative mechanisms for the changes in cortical volume and thickness are not known. Synaptogenesis, synaptic pruning, intracortical myelination, and connectivity may all exert an influence on volume and thickness during childhood and adolescence. Mutational or other developmental insults to cell populations or to molecular signaling systems that regulate the cell populations may lead to changes in cortical volume and thickness. However, MRI is an indirect measure of neuronal developmental processes, and any conclusion regarding an underlying mechanism or neuropathology of cortical volume and thickness decreases is speculative.

In conclusion, reduced volume in the anterior insular cortex and reduced volume and thickness in the posterior insular cortex seem to be shared structural brain phenotypes in young people with ASD (without mental retardation) and FEP, with no distinct insular deficits found in this study for either group. Insular abnormalities need further transdiagnostic study to determine their overlap/specificity across complex mental disorders.

Supplementary material

For supplementary material accompanying this paper visit https://doi.org/10.1017/S0033291717000988.

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Declaration of Interest

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Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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