RESEARCH ARTICLE

Neuroanatomical deficits shared by youth with autism spectrum disorders and psychotic disorders

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Abstract

Autism spectrum disorders (ASD) and early-onset psychosis (EOP) are neurodevelopmental disorders that share genetic, clinical and cognitive facets; it is unclear if these disorders also share spatially overlapping cortical thickness (CT) and surface area (SA) abnormalities. MRI scans of 30 ASD, 29 patients with early-onset first-episode psychosis (EO-FEP) and 26 typically developing controls (TD) (age range 10–18 years) were analyzed by the FreeSurfer suite to calculate vertex-wise estimates of CT, SA, and cortical volume. Two publicly available datasets of ASD and EOP (age range 7–18 years and 5–17 years, respectively) were used for replication analysis. ASD and EO-FEP had spatially overlapping areas of cortical thinning and reduced SA in the bilateral insula (all p 's < .00002); 37% of all left insular vertices presenting with significant cortical thinning and 20% (left insula) and 61% (right insula) of insular vertices displaying decreased SA overlapped across both disorders. In both disorders, SA deficits contributed more to cortical volume decreases than reductions in CT did. This finding, as well as the novel finding of an absence of spatial overlap (for ASD) or marginal overlap (for EOP) of deficits in CT and SA, was replicated in the two nonoverlapping independent samples. The insula appears to be a region with transdiagnostic vulnerability for deficits in CT and SA. The finding of nonexistent or small spatial overlap between CT and SA deficits in young people with ASD and psychosis may point to the involvement of common aberrant early neurodevelopmental mechanisms in their pathophysiology.

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KEYWORDS

autism spectrum disorder, cortical surface area, cortical thickness, first-episode psychosis, MRI, neurodevelopment

1 | INTRODUCTION

Autism spectrum disorder (ASD) and psychotic disorders represent two categories of neurodevelopment disorders that share aspects of genetics, environmental risk, clinical and cognitive symptomatology, and brain function. Individuals with ASD and psychotic disorders tend to present difficulties in tasks assessing social cognition, integration of information from the external and internal world, and perceiving/understanding one's self and others (Couture et al., 2010; Modinos, Renken, Ormel, & Aleman, 2011). It is unclear if a shared neuroanatomical deficit mediates these common cognitive deficits. However, volumetric decreases in the insula and cingulate cortex are consistently reported in ASD and psychotic disorders (Cheung et al., 2010) and these two cortical structures are thought to be part of the salience network responsible for coordinating the brain's response to external information (Uddin, 2015). Indeed, two meta-analyses demonstrated a cortical volume deficit in the bilateral anterior insula across a wide range of adult-onset psychotic and nonpsychotic psychiatric disorders and linked these observations to transdiagnostic network deficits in salience processing (Goodkind et al., 2015; McTeague et al., 2017). Although these meta-analyses did not include ASD, additional evidence based on transdiagnostic meta-analyses comparing ASD or psychotic disorders with other mental disorders further support that the insula might be a region especially vulnerable to transdiagnostic abnormalities in patients with psychiatric disorders (Carlisi et al., 2017; Cauda et al., 2018; Ellison-Wright & Bullmore, 2010).

Previous studies and meta-analyses conducted in either ASD or psychotic disorders have reported additional cortical and subcortical deficits in several regions, including frontal regions, the cingulum, the hippocampus, and the amygdala, among others (Bora et al., 2011; Ecker et al., 2013; Radua et al., 2012; Via, Radua, Cardoner, Happe, & Mataix-Cols, 2011). However, incongruent results have been reported when the neuroanatomy of individuals with ASD, psychotic disorders and typically developing subjects (TD) was directly (i.e., within-study, single scanner and acquisition protocol) compared (Katz et al., 2016; Mitelman et al., 2016; Parellada et al., 2017; Radeloff et al., 2014). The majority of these studies focused on adults and used volumetric brain measurements. Assessing youth with early-onset mental disorders during the first years of illness has the advantage of potentially reducing the effect of confounding factors such as years of education, pharmacological treatment or substance use, and longitudinal progressive effects of the disease on the brain (Fraguas, Diaz-Caneja, Pina-Camacho, Janssen, & Arango, 2016). Cortical volume results may be confounded by differential effects of its constituents: cortical thickness (CT) and surface area (SA). CT and SA are reported to be both highly heritable (heritability >80%) but appear to be influenced by

different sets of genes (Panizzon et al., 2009), have a differential correlation with cortical volume, with surface area showing a stronger relationship (Winkler et al., 2010), and contribute distinctively to cortical growth during early brain formation (Rakic, 1995). Spatially nonoverlapping alterations in CT and SA have previously been reported in ASD, suggesting that cortical volume alterations in ASD might be caused by separable variations in CT and SA (Ecker et al., 2013; Raznahan et al., 2012).

To the best of our knowledge, this is the first study that directly compares children and adolescents with ASD, early-onset first-episode psychosis (EO-FEP) and typically developing subjects (TD) to: (1) probe whether alterations in CT, SA, and volume overlap transdiagnostically; (2) examine whether in ASD and in EO-FEP alterations in CT and SA contribute equally to alterations in cortical volume; (3) whether in ASD and in EO-FEP, abnormalities in CT and SA do not spatially overlap.

Given prior reports of common volumetric deficits in ASD and psychotic disorders we hypothesized that ASD and EO-FEP would share alterations in CT and SA compared with TD. In addition, given previous reports of a low correlation between CT and SA in healthy individuals we expected that in both ASD and EO-FEP cortical volume deficits would have more spatial overlap with deficits in cortical surface area than thickness and that in both ASD and EO-FEP there would be no spatial overlap between abnormalities in CT and SA.

2 | METHODS

2.1 | Participants

2.1.1 | Sample 1: Children and adolescents with ASD, EO-FEP, and TD

We recruited 30 children and adolescents with ASD, 29 children and adolescents with EO-FEP (i.e., onset of positive symptoms before 18 years of age), and 26 TD matched for age, handedness and parental socioeconomic status (SES) for this study. The study was conducted at the Child and Adolescent Psychiatry Department at the Hospital Gregorio Marañón, Madrid, Spain. ASD patients were recruited through family associations and an outpatient clinic, and EO-FEP patients were recruited through inpatient or outpatient clinics at the time of their first episode of psychosis. TDs were recruited from the community, at publicly funded schools located in the same geographic area as the patients. The inclusion criteria for all patients were as follows (1) being 7–18 years of age at the first assessment, (2) speaking Spanish correctly, and (3) having a diagnosis of either (a) first-episode psychosis (i.e., presence of positive psychotic symptoms such as

delusions or hallucinations within a first-episode of psychosis of <24 months duration) or (b) a pervasive developmental disorder (PDD)—equivalent to the ASD category in former diagnostic classification systems (American Psychiatric Association, 2000). The inclusion criteria for TD were the same as for patients, except for having no current or previous psychiatric disorder. Exclusion criteria for all groups included (1) mental retardation per DSM-IV-TR criteria, (2) neurological disorders, (3) a history of head trauma with loss of consciousness, (4) pregnancy, (5) a concomitant Axis I disorder at the time of evaluation, and (6) fulfilling past or current diagnosis criteria of ASD in the EO-FEP group or of psychotic disorder in the ASD group.

Ethical considerations

The Institutional Review Board of Hospital Gregorio Marañón approved the study protocol and informed consent forms. All parents or legal guardians gave written informed consent after receiving complete information about the study; patients and TD agreed to participate.

Diagnostic assessment

Child psychiatrists with extensive experience in diagnosing ASD and psychosis conducted all diagnostic assessments, after direct interviews with the patients and their families and review of 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 individually to all participants and their parents in separate interviews, to obtain diagnoses in the EO-FEP patients and rule out concomitant psychiatric disorders in all groups. Patients were included in the EO-FEP group if they fulfilled any DSM-IV-TR diagnosis of psychotic disorder (other than drug-induced psychosis) after K-SADS-PL assessment. 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. Qualified ADOS research-trained child psychiatrists administered the Autism Diagnostic Observation Schedule—Generic (ADOS-G) (Lord et al., 2000) when the initial diagnosis was not clear (5 cases). The final diagnosis was based on best clinical judgment considering all the available information (Volkmar et al., 2014).

Clinical and cognitive assessment

Parental SES was estimated using the Hollingshead–Redlich scale (Hollingshead & Redlich, 1958). Handedness was assessed with item 5 of the Neurological Evaluation Scale (Buchanan & Heinrichs, 1989). An estimated intelligence quotient (IQ) was calculated in EO-FEP and TD using the vocabulary and block design tests of the Wechsler Intelligence Scale for Children (WISC-R), or the Wechsler Adult Intelligence Scale (WAIS-III), as appropriate (Wechsler, 1997, 2003). A full scale IQ was obtained in the ASD group because the estimated IQ has been found to be less reliable in this group (Merchan-Naranjo et al., 2012). The Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987; Peralta & Cuesta, 1994) was administered to both patient groups and PANSS positive, negative, general, and total

subscores were computed. Intraclass correlation coefficients for PANSS inter-rater reliability were above 0.8. For both patient groups, the cumulative antipsychotic dose at the baseline visit (converted to chlorpromazine equivalent doses) was computed (Andreasen, Pressler, Nopoulos, Miller, & Ho, 2010; Rijcken, Monster, Brouwers, & de Jong-van den Berg, 2003).

2.1.2 | Sample 2: ASD and TD

Sample 2 was drawn from the NYU Langone Medical Center Sample, which is a subsample from the Autism Brain Imaging Data Exchange (ABIDE, 2017) repository (NYU Langone Medical Center sample) (Di Martino et al., 2014). Seventy-nine participants with Autism Spectrum Disorders (age 7.1–39.1 years) and 105 typically developing controls (TD) (age 6.5–31.8 years) were recruited in the New York City and surrounding areas through referrals from the NYU Child Study Center clinical services, as well as through leaflets, advertisements and parent support groups. Written informed consent/assent was obtained for all participants and their parents/legal representatives, as appropriate. Exclusion criteria for both groups were as follows: (i) current chronic systemic medical conditions, (ii) contraindications to MRI scanning, (iii) pregnancy, and (iv) use of antipsychotics. The ASD group included patients with DSM-IV-TR diagnoses of Autistic Disorder, Asperger's Disorder, or Pervasive Developmental Disorder Not-Otherwise-Specified, based on review of available records and the participant's history, diagnostic interview with the Autism Diagnostic Observation Schedule (ADOS), and an Autism Diagnostic Interview—Revised (ADI-R), when possible. All participants underwent a diagnostic assessment for Axis-I disorders with the K-SADS-PL in participants aged less than 18 years, or the Structured Clinical Interview for DSM-IV-TR Axis-I Disorders, Nonpatient Edition (SCID-I/NP) and the Adult ADHD Clinical Diagnostic Scale (ACDS) in adults. Age and sex-matched TD were included if they did not meet criteria for any current Axis-I disorders after the diagnostic assessment. A current diagnosis (<3 months prior to the evaluation) of manic or depressive episode, bipolar disorder, schizophrenia, or posttraumatic stress disorder was an exclusion criterion for ASD participants. Additional assessments included the four subtests of the Wechsler Abbreviated Scale of Intelligence (WASI), the Social Communication Questionnaire, the Social Responsiveness Scale (SRS) and the Vineland Adaptive Behavior Scales—Second Edition (VABS). Current medication status and whether participants were taking stimulants on the day of the scan was recorded. For further details, please see: http://fcon_1000.projects.nitrc.org/indi/abide/abide_I.html.

The ABIDE initiative provides pre-processed quality controlled (three independent ratings) neuroanatomical data (<http://preprocessed-connectomes-project.org/abide/>). From the “NYU” data that was approved by all raters, we first selected all subjects younger than 19 years. Second, the group of subjects that were aged less than 19 years entered in a permutation-based matching algorithm to individually match patients and TD for age and sex. The final sample included 53 subjects with ASD and 53 TD aged 7–18 years.

2.1.3 | Sample 3: EOP and TD

Sample 3 was drawn from the Child and Adolescent NeuroDevelopment Initiative (CANDI) share repository (Kennedy et al., 2012). In brief, patients with a lifetime diagnosis of DSM-IV bipolar disorder with psychotic features, schizophrenia or schizoaffective disorder aged 6–17 were recruited from inpatient and outpatient facilities from the McLean Hospital and Cambridge Health Alliance programs and advocacy groups. Typically developing controls (TD) with no history of DSM-IV Axis-I disorders were recruited through advertisements. Exclusion criteria for patients and TD included (i) full IQ < 70, (ii) major sensorimotor handicaps, (iii) history of learning difficulties, autism, eating disorders, or alcohol use disorders (in the 2 months prior to the scan or total past history ≥ 12 months), (iv) history of electroconvulsive therapy, (v) active medical disease, (vi) contraindications to acquire MRI (e.g., claustrophobia, metal devices), and (vii) current pregnancy or lactation. All children underwent a clinical assessment by consultant child psychiatrists using the K-SADS-Epidemiologic version (K-SADS-E). An indirect K-SADS-E was also administered to their parents. Clinical and functional measures included the Mania Rating Scale (MRS) including the psychosis items, and the Global Assessment of Functioning (GAF). Written informed consent/assent was obtained for all participants and their parents/legal representatives, as appropriate. For further details, please see Frazier et al. (2008).

All participants with EOP [i.e., early-onset schizophrenia spectrum illness (EO-SZ), early-onset bipolar disorder with psychotic features (EO-BP)] and TD available in the repository were included. The final sample included 39 subjects with EOP and 29 TD aged 5–17 years.

2.2 | MRI acquisition and image analysis

Sample 1 was acquired on a 1.5 T Philips Intera scanner, sample 2 on a 3 T Siemens Allegra and sample 3 on a 1.5 T General Electric Signa scanner. Further details about the acquisition protocols are given in Supporting Information Table S1.

Image processing

The image quality of the raw T1-weighted images was assessed with the Image Quality Rating (IQR). The IQR is a weighted average of the Noise Contrast Ratio, Inhomogeneity Contrast Ratio, and root mean square resolution (see <http://dbm.neuro.uni-jena.de/cat/index.html#QA>). The IQR is defined as a percentage range and all T1-weighted images rated in the good to satisfactory range (i.e., IQR ≥ 70 , see Supporting Information Table S1 in the Supporting Information Material). An experienced user (JJ) checked visually the FreeSurfer output using the FreeSurfer QA tool (v5.3, <http://surfer.nmr.mgh.harvard.edu/fswiki/QATools>). Manual editing was done if necessary and FreeSurfer output was regenerated using the edited input (all edits related to skull-strip errors).

All participants' images were analyzed using the FreeSurfer analysis suite (v5.3) with default settings to provide detailed anatomical information customized for each individual (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999). The FreeSurfer analysis stream includes intensity bias field removal, skull stripping, construction of gray and white matter surfaces (Fischl et al.,

2002; Segonne et al., 2004), and vertex-wise maps of cortical thickness (CT), surface area (SA) and volume (CVOL) (Fischl & Dale, 2000). A nonlinear surface-based inter-subject registration procedure aligns the cortical folding patterns of each subject to a standard surface ("fsaverage") space (Fischl, Sereno, Tootell, & Dale, 1999). To enable vertex-wise comparisons across subjects, the CT, SA, and CVOL maps must be resampled into the standard space. The resampling of SA and CVOL includes a "Jacobian correction" (similar to that described in Winkler et al., 2012) to account for any surface stretching or compression during the registration process. This correction is not needed for CT because it is measured along a vector normal to any stretching or compression. The registration procedure provides vertex-wise SA and CVOL estimates of the relative areal expansion/compression of each location in standardized space. Before statistical analyses, standard space maps of CT, SA, and CVOL were smoothed with a surface-based kernel with a full-width at half maximum of 15 mm. Measurements of total brain volume, mean whole brain CT and total SA were derived for each participant in the native anatomical space. For illustrative purposes we "inflated" the highly-folded surfaces to allow for visualization inside the sulci. The left and right hemispheres were analyzed separately.

2.3 | Statistical analyses

Demographic and clinical variables were compared between diagnostic groups using parametric or nonparametric tests as appropriate. The chlorpromazine equivalent dose distribution was heavily skewed and was therefore transformed using a Box-Cox transformation.

2.3.1 | Between-group differences in CT, SA, and CVOL (samples 1, 2, and 3)

In order to avoid systematic differences between groups due to, for example, scanner vendor, imaging protocols, scan resolution, sample characteristics, and field strength (Chalavi, Simmons, Dijkstra, Barker, & Reinders, 2012; Govindarajan, Freeman, Cai, Rahbar, & Narayana, 2014; Han et al., 2006; Narayana et al., 2012; Tummala et al., 2016), the following pair-wise comparisons between diagnostic groups [ASD vs. TD (in sample 1 and in sample 2); EO-FEP vs. TD (sample 1); ASD vs. EO-FEP (sample 1); EOP vs. TD (sample 3)] were performed.

The maps of CT, SA, and CVOL in standard space were parcellated using a modified Desikan–Killany parcellation scheme (Desikan et al., 2006) (see Supporting Information Figure S1), resulting in 29 regions for each hemisphere. In each region, between-group differences for each type of measurement were estimated using linear regression within a general linear model (GLM) framework, with age, sex and total brain volume as covariates. Results were corrected for multiple comparisons utilizing a simulation procedure implemented in FreeSurfer (Hagler, Saygin, & Sereno, 2006). This procedure includes the following steps: First, the initial vertex-wise threshold was set to $p = .05$ to form spatially contiguous areas of association (referred to as "cluster"). Secondly, the likelihood that a significant finding (cluster) of at least the minimal observed size and magnitude (as specified by the vertex-wise

TABLE 1 Demographic, clinical, and whole brain characteristics of the three nonoverlapping independent samples

	Sample 1			Sample 2			Sample 3		
	ASD N = 30	EO-FEP N = 29	TD N = 26	ASD N = 53	TD N = 53	TD N = 53	EOP N = 39	TD N = 29	p
Age, Years, mean (SD)	13.3 (1.99)	14.1 (0.98)	13.1 (2.43)	11.3 (2.83)	11.8 (2.75)	11.8 (2.75)	12.6 (2.68)	10.5 (2.90)	.01
Sex, % male	93.3%	62.1%	96.2%	76%	76%	76%	51%	59%	.55
Parental years of education, mean (SD)	14.2 (3.1)	13.3 (4.2)	14.0 (3.4)						
Parental socio-economic status, mean (SD)	3.5 (1.4)	2.8 (1.3)	3.5 (1.2)						
Socio-economic status, % low (I–III)	53%	63%	56%				57%	24%	
IQ, Total score, mean (SD)	88 (18.1)	87 (25.6)	113 (15.3)	107 (17.6)	116 (13.0)	116 (13.0)	100 (13.5)	115 (12.7)	<.001
GAF score, mean (SD)	48.07 (12.2)	47.2 (15.9)	92.6 (5.6)				48.2 (4.5)	68.3 (2.7)	<.001
Psychotic symptoms. Score, mean (SD)									
PANSS positive	11.1 (4.4)	22.5 (7.0)							<.001
PANSS negative	19.6 (6.1)	21.4 (8.8)							.39
PANSS general	34.8 (8.7)	43.0 (13.4)							<.01
PANSS total	65.3 (15.9)	87.7 (27.6)							<.001
ADI/ADOS, mean (SD)									
ADI verbal				15.7 (4.2)					
ADI social				19.3 (5.4)					
ADI RRB				5.7 (2.5)					
ADI early onset				3.3 (1.4)					
ADOS communication				3.5 (1.6)					
ADOS social				7.8 (2.9)					
ADOS RRB				2.7 (1.5)					
ADOS total				11.3 (4.1)					
Mania rating scale (MRS)							18.2 (4.6)	1.7 (3.4)	
MRS psychosis subscale							5.7 (4.8)	0.5 (1.6)	
Antipsychotic cumulative dose, Chlorpromazine equivalents (milligrams), median (range)	0 (0–682)	2,648.6 (0–89,875)							<.001
Current antipsychotic treatment, N (%)	8 (26.6%)	27 (93.0%)					35 (90%)		<.001
Whole brain morphological measurements									
Volume (cm ³)	1,175.3 (102.2)	1,120.0 (136.7)	1,160.6 (113.3)	1,206.8 (142.4)	1,231.1 (125.2)	1,231.1 (125.2)	9,035.4 (86.4)	9,183.7 (96.8)	.51
Cortical thickness (mm)	2.52 (0.1)	2.53 (0.1)	2.55 (0.2)	2.89 (0.1)	2.94 (0.2)	2.94 (0.2)	2.74 (0.1)	2.78 (0.1)	.21
Cortical surface area (cm ²)	1,855.7 (181.4)	1,759.7 (218.1)	1,844.1 (164.2)	1,788.7 (184.8)	1,770.2 (168.5)	1,770.2 (168.5)	1,527.23 (138.5)	1,549.6 (179.5)	.56

ADI = autism diagnostic interview; ADOS = autism diagnostic observation schedule; ASD = autism spectrum disorder; EO-FEP = early-onset first episode psychosis; EOP = early-onset psychosis; GAF = global assessment of functioning; IQ = intelligence quotient; PANSS = positive and negative syndrome scale; RRB = restrictive and repetitive behaviors; TD = typically developing subjects.

threshold) would appear by chance, that is, when using repeated random sampling, was tested using Monte-Carlo simulation with 10,000 iterations. This results in a cluster-wise probability (CWP) representing the likelihood that the corresponding clusters appeared by chance. To correct for multiple comparisons, an observed cluster was considered statistically significant if its CWP was below the threshold of 0.00172, that is, 0.05 divided by 29, the number of regions per hemisphere.

2.3.2 | Hypothesis 1

Transdiagnostic overlap of cortical thickness and surface area deficits with respect to TD (sample 1).

The multiple-comparison-corrected statistical maps representing group differences in CT and SA were used to quantify whether the two disorders had spatially overlapping alterations with respect to TD. The percentage transdiagnostic overlap $O_{ASD-EO-FEP}$ for each region was defined as:

$$O_{ASD-EO-FEP} = \left(\frac{\text{Number of vertices with alterations in both ASD and EO-FEP}}{\text{Number of vertices with alteration in ASD, EO-FEP, or both}} \right) \times 100\%$$

To assess whether $O_{ASD-EO-FEP}$ was higher than expected by chance we simulated clusters for CT and SA with the observed cluster sizes following a strategy similar to (Ecker et al., 2013). The spatial location and shape of the clusters were randomly chosen for each disease group while the sizes of the clusters were fixed to the ones that were observed in the study. This process was repeated 50,000 times in order to create a probabilistic null distribution representing the shared spatial overlap of ASD and EO-FEP groups (i.e., the Dice Similarity Index).

For the areas of the significant clusters where both ASD and EO-FEP displayed significant CT or SA abnormalities, that is, areas of transdiagnostic overlap, mean CT, or total SA were calculated. Pearson correlation coefficients were computed between the residuals of the mean CT and total SA (by regressing out age, sex, and total brain volume) and (1) the PANSS positive, negative, general and total scores in the combined patient sample (ASD + EO-FEP), (2) IQ (in the ASD and EO-FEP groups), and (3) transformed cumulative chlorpromazine equivalents in the individuals who were using antipsychotic medication [35 (8 ASD + 27 EO-FEP) subjects]. These results were not corrected for multiple comparisons given the exploratory nature of these analyses.

2.3.3 | Hypothesis 2

Across diagnoses, disorder-associated alterations in cortical volume display more spatial overlap with alterations in cortical surface area than with abnormalities in thickness (samples 1, 2, and 3).

Within each sample, it was examined whether significant clusters displaying abnormalities in CVOL spatially overlapped with significant clusters of abnormalities in CT and/or SA. We first calculated for each individual the CT-CVOL and/or SA-CVOL overlap, that is, the percentage spatial overlap between CT or SA alterations and CVOL alterations:

$$O_{CT-CVOL} = \left(\frac{\text{Number of vertices with alteration in CT and CVOL}}{\text{Number of vertices with alteration in CVOL}} \right) \times 100\%$$

$$O_{SA-CVOL} = \left(\frac{\text{Number of vertices with alteration in SA and CVOL}}{\text{Number of vertices with alteration in CVOL}} \right) \times 100\%$$

For each individual the OCT-CVOL and OSA-CVOL percentages were averaged over both hemispheres to get an estimation of global OCT-CVOL and OSA-CVOL per subject. Global OCT-CVOL and OSA-CVOL were entered in Z-tests for comparing proportions to assess whether the global OCT-CVOL, OSA-CVOL differed significantly between groups (Moore, Notz, & Fligner, 2013).

2.3.4 | Hypothesis 3

Across diagnoses, abnormalities in CT and SA do not spatially overlap (samples 1, 2, and 3).

The same analytic protocol as for hypothesis two was implemented. For each subject we calculated the percentage spatial overlap between CT and SA (OCT-SA), which was defined as:

$$O_{CT-SA} = \left(\frac{\text{Number of vertices with alteration in CT and SA}}{\text{Number of vertices with alteration in CT, SA, or both}} \right) \times 100\%$$

After averaging over hemispheres, the global OCT-SA was entered in Z-tests for comparing proportions to assess whether it differed significantly between groups (Moore et al., 2013).

3 | RESULTS

Demographic and clinical characteristics and whole brain measurements of CT, SA, and CVOL for the three study samples are presented in Table 1 (see Supporting Information Tables S3, S4, and S5 for additional sample characteristics).

Hypothesis 1: *Transdiagnostic overlap of cortical thickness and surface area deficits with respect to TD (sample 1).*

Figure 1 shows the significant clusters where ASD (red) and EO-FEP (green) had decreased values in CT and SA with respect to TD, as well as shared, that is, transdiagnostic, deficits (yellow). The two disorders shared cortical thinning in the left insular cortex and right insular, superior frontal and temporal cortices. Shared decreases in SA were present in the bilateral insular cortex (see Figure 1). Regarding the spatial overlap of these findings, only the transdiagnostic overlap $O_{ASD-EO-FEP}$ for CT in the left insular cortex and for SA in the bilateral insular cortex was considerably and significantly larger than the maximum observed overlap from 50,000 simulations (left CT: observed overlap $O_{ASD-EO-FEP} = 37\%$, simulated overlap = 9%; left SA: observed overlap = 20%, simulated overlap = 13%; right SA: observed overlap = 61%, simulated overlap = 20%; all three p 's < .00002, see also Supporting Information Figure S2). Supporting Information Figure S3 shows an example (SA in the right insular cortex) of transdiagnostic differences.

To assess whether CT and SA were affected differently in ASD compared with EO-FEP we first summed all vertices of significant clusters in CT or SA, from the ASD versus TD and EO-FEP versus TD comparisons. From the total amount of vertices showing reduced CT, a higher proportion belonged to EO-FEP (ASD: 49%; EO-FEP: 51%, $Z = 3.7$, $p < .0005$). From the total amount of vertices displaying

FIGURE 1 Cortical thickness and surface area reductions in ASD and EO-FEP. Deficits in the ASD and/or EO-FEP groups when compared with the TD group. The percentages indicate the shared overlap $O_{ASD-EO-FEP}$ per cluster for cortical thickness and surface area defined as: $O_{ASD-EO-FEP} = \left(\frac{\text{Number of vertices with alterations in both ASD and EO-FEP}}{\text{Number of vertices with alteration in ASD, EO-FEP, or both}} \right) \times 100\%$. ASD, autism spectrum disorder; EO-FEP, early-onset first-episode psychosis; TD, typically developing subjects [Color figure can be viewed at wileyonlinelibrary.com]

reduced SA, a higher percentage belonged to ASD (ASD: 54%; EO-FEP: 46%, $Z = 17.5$, $p < .0005$). When we repeated the same analysis for the vertices in the insula cortex only, ASD had a higher percentage of deficits in CT (ASD: 55%; EO-FEP: 45%, $Z = 8.1$, $p < .0005$) and SA (ASD: 53%; EO-FEP: 47%, $Z = 6.2$, $p < .0005$).

The vertex-wise maps of t-values demonstrated that CT and SA decreases in ASD and EO-FEP groups were subtle (see Supporting Information Figures S4 and S5). As can be seen in Figure 1, in the ASD group, reductions in CT or SA encompassed inferior frontal, inferior parietal, temporal, and cingulate regions. In the EO-FEP group, decreases were located in cingulate, superior temporal, inferior frontal, and post central regions. No significant increases in CT and SA were found in ASD and EO-FEP groups compared with TD.

With regard to the relationship with clinical symptoms, it was observed that the mean CT of the left insular cluster, calculated over all vertices where ASD and EO-FEP showed a decrease, correlated negatively with the PANSS general score ($r = -0.27$, $p = .04$; see Supporting Information Figure S6). There were no other significant correlations (all $p > .14$).

There were no significant correlations between mean CT or total SA in the significant clusters and cumulative chlorpromazine equivalents in the group of individuals who were using antipsychotic medication. In both ASD and EO-FEP, there were also no significant associations between any of the findings and IQ.

When compared with each other, both ASD and EO-FEP had distributed clusters of differences in CT and SA. ASD had less CT or SA in anterior temporal, middle frontal, and medial parietal regions and EO-FEP had less CT or SA in middle frontal, cingulate, inferior parietal and temporal regions (see Supporting Information Figure S7).

Hypothesis 2: Across diagnoses, disorder-associated alterations in cortical volume display more spatial overlap with alterations in cortical surface area than with abnormalities in thickness (samples 1, 2, and 3).

For sample 1, there were an equal number of clusters containing overlapping CVOL and CT deficits and overlapping CVOL and SA deficits in ASD (6 clusters) and EO-FEP (8 clusters), see Figure 2 and Supporting Information Table S6. The global O_{CT-VOL} was smaller than the global O_{SA-VOL} in both ASD and EO-FEP groups (ASD: global O_{CT-VOL} 51% vs. global O_{SA-VOL} 63%; $Z = 24.1$, $p < .0005$, EO-FEP: global O_{CT-VOL} 34% vs. global O_{SA-VOL} 56%; $Z = 43.4$, $p < .0005$). For both nonoverlapping independent samples of subjects with ASD and EOP the number of clusters with overlapping CVOL and CT deficits was considerably smaller than the number of clusters with CVOL and SA [sample 2 (ASD): 2 CVOL-CT clusters, 6 CVOL-SA clusters; sample 3 (EOP): 7 CT-CVOL clusters, 14 CVOL-SA clusters, see Figure 2 and Supporting Information Table S6]. For both independent samples the global O_{CT-VOL} was considerably lower than the global O_{SA-VOL} (sample 2: global $O_{CT-VOL} = 69\%$, global $O_{SA-VOL} = 76\%$; $Z = 9.4$, $p < .0005$, sample 3: global $O_{CT-VOL} = 50\%$, global $O_{SA-VOL} = 66\%$; $Z = 30.9$, $p < .0005$).

Hypothesis 3: Across diagnoses, abnormalities in CT and SA do not spatially overlap (samples 1, 2, and 3).

In sample 1 O_{CT-SA} was 0% in the ASD group and in the EO-FEP group CT and SA deficits only overlapped in the left posterior insular and right posterior superior temporal cortex with O_{CT-SA} 16% and 22%, respectively (see Figure 3). In sample 2 (ASD) O_{CT-SA} was 0% and in sample 3 (EOP) O_{CT-SA} was 22% in the right posterior superior temporal cortex (see Figure 3). The correlations between mean CT and total SA calculated over the overlapping areas across individuals were low in the EO-FEP and EOP groups (all r 's < 0.12 , $p > .5$, see Supporting Information Figure S8 as an example).

4 | DISCUSSION

The first study comparing cortical morphology among children and adolescents with ASD, EO-FEP, EOP, and TD had three main findings, (1) individuals with ASD or EO-FEP had spatially-overlapping reductions both in CT and in SA in the insular cortex which were significantly larger than as expected by chance; (2) in individuals with ASD, EO-FEP, or EOP decreases in SA contributed more to CVOL reductions than decreases in CT did; and (3) deficits in CT and SA did not

FIGURE 2 Spatial overlap between decreases in cortical volume, thickness, and surface area in ASD, EO-FEP, and EOP. ASD, autism spectrum disorder; EO-FEP, early-onset first-episode psychosis; EOP, early-onset psychosis [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 3 Spatial overlap between decreases in cortical thickness and surface area in ASD, EO-FEP, and EOP. The percentages indicate the spatial overlap $O_{CT-SA}:O_{CT-SA} = \left(\frac{\text{Number of vertices with alteration in CT and SA}}{\text{Number of vertices with alteration in CT, SA, or both}} \right) \times 100\%$. ASD, autism spectrum disorder; EO-FEP, early-onset first-episode psychosis; EOP, early-onset psychosis [Color figure can be viewed at wileyonlinelibrary.com]

spatially overlap in subjects with ASD and only marginally in individuals with EO-FEP and EOP.

We previously reported on a transdiagnostic anterior and posterior insular volume deficit in the ASD and EO-FEP sample (sample 1) (Parellada et al., 2017). The current study extends these findings by showing that insular volume deficits are caused by decreases in SA and, to a lesser degree, by deficits in CT and that these two types of deficits are largely independent (i.e., spatial nonoverlap) from each other. Our finding of a spatial nonoverlap of SA and CT deficits in ASD replicates previous reports in pre-schoolers and adults with high functioning ASD (Ecker et al., 2013; Raznahan et al., 2012). The present study is the first one to show minimal overlap in children and adolescents with EO-FEP and EOP. The non-overlap of CT and SA deficits may arise in early neurodevelopment as CT and SA are thought to stem from independent cellular determinants (Rakic 1995). However, MRI is an indirect measure of neuronal developmental processes and any conclusions regarding the underlying mechanisms or neuropathology of CT and SA deficits are necessarily speculative. Notwithstanding, the current results suggest that shared ASD-EO-FEP decreases in insular volume are caused by shared reductions in CT and SA which are largely independent from each other. Although our findings could also be interpreted as the result of increased CT and SA in the TD group, their replication in the independent samples provides additional support for the presence of reduced CT and SA in the clinical groups relative to TD. Even if the clinical significance of our findings remains to be elucidated, the shared patterns found in both disorders strongly suggest the involvement of similar neurodevelopmental mechanisms in their pathophysiology.

The current study presented widespread insular volume deficits in ASD and EO-FEP and these are in keeping with both posterior and anterior insular volume deficits reported in ASD and psychotic disorders (Cheung et al., 2010; Goodkind et al., 2015). To further assess the consistency of our results we mapped our volumetric insular results to those reported by (Goodkind et al., 2015) and found an inter-study overlap of 520 ml in the right insula (see Supporting Information Figure S9). Whether the transdiagnostic decreases in CT drive shared ASD-EO-FEP symptomatology remains unclear as we only found a moderate relationship between deficits in the left insula and general psychopathology as measured by PANSS. Broad neuropsychological impairment is characteristic of major mental disorders (Snyder, Miyake, & Hankin, 2015) and may be linked to the insula via the salience network (Uddin & Menon, 2009). Indeed, abnormal activation of the anterior insula in salience processing was found across major psychiatric disorders, which complements prior findings of transdiagnostic insular volume deficits (Goodkind et al., 2015; McTeague et al., 2017; Uddin, 2015). EO-FEP and ASD also had unique, widespread, noninsular reductions in CT and SA. Reductions in CT or SA in the ASD group included inferior frontal, inferior parietal, temporal, and cingulate regions, while decreases were located in cingulate, superior temporal, inferior frontal, and post central regions in EO-FEP patients. These findings are overall consistent with previous reports of widely distributed decreases in CT and SA in both ASD and EO-FEP in similar regions (Ecker et al., 2013; Radua et al., 2012). The uncorrected vertex-wise t-maps displayed moderate effects and underscore the

notion of ASD and EO-FEP as disorders in which distributed brain networks are affected in a complex manner, rather than single cortical regions with large effect sizes (Ecker et al., 2013; Satterthwaite & Baker, 2015). This is the first study, to the best of our knowledge, to directly compare CT and SA between ASD and EO-FEP groups. Different early neurodevelopmental maturational patterns, that is, an early overgrowth of cortical surface area in ASD and undergrowth in children with schizophrenia (Baribeau & Anagnostou, 2013) has been reported. However, whether possible early life maturational differences lead to the observed divergent patterns in late childhood and thereafter can only be confirmed with longitudinal transdiagnostic studies.

There are several limitations to this study that should be considered when interpreting the results. First, the ASD and EOP samples were hard to acquire, thus leading to relatively small sample sizes. It may be that we were only able to detect significant findings in the regions with the greatest group differences (e.g., insula) and that similar patterns might be detected in other brain areas using larger samples. Nevertheless, our main results were replicated in two other publicly available datasets, thus supporting the consistency of our findings. Second, our findings pertain to a specific subpopulation of individuals within a specific narrow age range, and may not straightforwardly generalize to older populations. Third, the patient groups were not perfectly matched to their respective TD group. Lower IQ and an increased male : female ratio are typical of psychotic disorders and more so of ASD (Chisholm, Lin, Abu-Akel, & Wood, 2015). This complicates the issue of group matching for these variables. However, IQ did not correlate significantly with any of the morphological deficits and we controlled for sex in all analyses. Fourth, the vertex-wise surface area and volumetric measurements investigated in the present study were based not on absolute measurements but rather on areal expansion or contraction relative to a template.

The findings of this study mark diverse structural pathology in the insula as a shared phenotype in young people with ASD and EO-FEP. The low coupling between decreases in CT and SA suggest that these measurements reflect the outcome of differential neurodevelopmental processes, which contribute to largely independent decreases in CT and SA in both disorders.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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