

RESEARCH ARTICLE

# Altered Cortico-Striatal Connectivity in Offspring of Schizophrenia Patients Relative to Offspring of Bipolar Patients and Controls

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## Abstract

Schizophrenia (SZ) and bipolar disorder (BD) share clinical features, genetic risk factors and neuroimaging abnormalities. There is evidence of disrupted connectivity in resting state networks in patients with SZ and BD and their unaffected relatives. Resting state networks are known to undergo reorganization during youth coinciding with the period of increased incidence for both disorders. We therefore focused on characterizing resting state network connectivity in youth at familial risk for SZ or BD to identify alterations arising during this period. We measured resting-state functional connectivity in a sample of 106 youth, aged 7–19 years, comprising offspring of patients with SZ ( $N = 27$ ), offspring of patients with BD ( $N = 39$ ) and offspring of community control parents ( $N = 40$ ). We used Independent Component Analysis to assess functional connectivity within the default mode, executive control, salience and basal ganglia networks and define their relationship to grey matter volume, clinical and cognitive measures. There was no difference in connectivity within any of the networks examined between offspring of patients with BD and offspring of community controls. In contrast, offspring of patients with SZ showed reduced connectivity within the left basal ganglia network compared to control offspring, and they showed a positive correlation between connectivity in this network and grey matter volume in the left caudate. Our findings suggest that dysconnectivity in the basal ganglia network is a robust correlate of familial risk for SZ and can be detected during childhood and adolescence.

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## Introduction

Schizophrenia (SZ) and bipolar disorder (BD) share genetic risk factors [1, 2], clinical symptoms [3], cognitive deficits [4], and brain structural and functional alterations [1, 5–7].

Resting-state functional magnetic resonance imaging (rs-fMRI) has enabled the study of the brain's intrinsic functional architecture [8]. In the present study we focus on resting-state networks (RSN) that are reliably identified across samples and are also implicated in both disorders [9–12, 7].

The default mode network (DMN) comprises the medial prefrontal cortex, posterior cingulate/precuneus, lateral temporal cortex and inferior parietal lobule [13], and is deactivated during cognitive processes requiring externally oriented attention [14]. Aberrant connectivity within the DMN has been observed in adult [15] and adolescent SZ patients [16]. Studies in adult BD have reported conflicting results with either no abnormalities [17] or hypo-connectivity in the DMN [18]. The executive control network (ECN), which includes the dorsolateral prefrontal and posterior parietal cortices [19], is implicated in planning, decision making and sustained attention [20]. Reduced ECN connectivity has been observed in adult SZ patients [21], while hyperconnectivity has been reported in paediatric BD [22]. The salience network (SN) includes the fronto-insular cortex and the dorsal anterior cingulate, and has a role in emotional processing [19]. Studies in adult SZ have shown hypoconnectivity within this network [15], while it may be increased in BD [17]. In the basal ganglia network (BGN), which includes the striatum, inferior frontal gyri and thalami, similarly reduced connectivity has been reported in both SZ and BD [23, 24].

Connectivity within the DMN has been found to be increased in adult unaffected SZ relatives [25–27] and decreased in BD relatives [28]. For the ECN, a recent report found reduced connectivity within the right inferior frontal gyrus in young adult offspring of patients with a psychotic spectrum disorder [29] while the only study in young offspring of BD patients so far revealed increased connectivity in the ventrolateral prefrontal cortex [30]. A recent study in adult relatives of patients with first episode psychosis has also reported hypoconnectivity within the BGN [31]. To our knowledge the Bipolar and Schizophrenia Network on Intermediate Phenotypes study is the only study to date to compare RSN between adult relatives of SZ or BD comparatively [28, 11, 24], and has reported reduced connectivity within the frontal/thalamic/basal ganglia network in relatives of SZ or BD probands, with a more prominent decrease in striatal connectivity for SZ relatives.

The evidence summarized above indicates that abnormal functional connectivity in SZ and BD may be related to familial risk. RSN undergo substantial reorganization throughout childhood and adolescence [32], during which there is a shift in the balance between prefrontal and subcortical connectivity [33]. The engagement of the prefrontal cortex approaches adult levels early in adolescence [34] while striatal networks experience significant maturation throughout adolescence and into adulthood [35]. Studies employing neuropsychological measures have revealed that child and adolescent offspring of patients with SZ (SzO) or BD (BpO) share difficulties in verbal and visual episodic memory, executive function and intelligence [36, 37], although group specific impairment has also been described [37]. However, no study so far has examined intrinsic connectivity of resting state networks implicated in cognition in young offspring of patients with SZ or BD.

In this context, we set out to test whether intrinsic functional connectivity of cortical and cortico-subcortical networks occurring during childhood and adolescence are disrupted by familial risk of SZ or BD. We hypothesized that young offspring of SZ or BD patients would show abnormal intrinsic connectivity in regions where dysconnectivity has been reported in adult patients or relatives of SZ and BD, namely frontal and frontostriatal areas. To address

this hypothesis we used Independent Component Analysis (ICA) to identify the DMN, ECN, SN and BGN in a sample of child and adolescent offspring. Our further aim was to examine the relationship between resting state connectivity differences and grey matter volume, cognitive and clinical measures.

## Materials and Methods

This study has been approved by the Comitè Ètic d'Investigació Clínica (CEIC), Hospital Clínic, Barcelona, Spain. For participants aged under 18, parents provided written informed consent and participants older than 12 provided assent. Participants aged 18 and over gave written informed consent. Families received compensation for their time and travel expenses.

## Subjects

This study was undertaken at the Child and Adolescent Psychiatry and Psychology Department of the Hospital Clinic of Barcelona, Spain.

Psychiatrists of adult inpatient and outpatient units were asked to identify BD and SZ patients who had children aged 7 to 19 years. Exclusion criteria for index parents were: intellectual disability, and drug or medically-induced psychosis or mania. 58 families (31 BD and 27 SZ) were assessed. Community control parents were recruited through advertisements posted in the community within the same geographical area as patients. Exclusion criteria for community control parents were: intellectual disability, severe neurological conditions, and personal or 1st degree family history of SZ or BD spectrum disorders. In order to reduce selection bias, parents who stated to be specifically motivated to participate due to concerns about school performance or emotional or behavioural problems in their offspring were also excluded. 32 control families met inclusion criteria.

Exclusion criteria for all offspring included: intellectual disability according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association, APA, 1994, [38]) criteria (IQ below 70 and impaired functioning), history of head injury with loss of consciousness or severe neurological conditions. Additionally, CC-offspring had no personal, 1st or 2<sup>nd</sup> degree family history of SZ or BD spectrum disorders. Thirty-three SZ-offspring, 47 BD-offspring and 46 offspring of community control parents (CC-offspring) were recruited. Further information on the recruitment of the sample is provided in Sánchez-Gistau and colleagues [39].

## Clinical/cognitive assessments

Clinical and cognitive assessments were carried out by experienced psychiatrists and psychologists at the Child and Adolescent Outpatient Department of the hospital. Parental and offspring interviews were conducted by different team members, each blind to the others' assessment. Parental socioeconomic status (SES) was estimated using the Hollingshead Scale [40]; considering the highest SES among both parents. Clinical diagnoses were based on the Spanish version of the Structured Interview for DSM-IV disorders (SCID) [41] for parents and offspring aged 18 years or older. Offspring under 18 were assessed by child and adolescent psychiatrists using the Spanish version of The Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime version (K-SADS-PL) [42] administered separately to parents and children. Details on past or current psychopharmacological treatments were also registered.

Symptoms were evaluated with the Scale of Prodromal Symptoms (SOPS) within the Structured Interview for Prodromal Symptoms [43], the Young Mania Rating Scale [44] and the Hamilton Depression Rating Scale [45]. Overall clinical severity was assessed with the Clinical

Global Impression index [46] and functionality with the Global Assessment of Functioning scale from DSM-IV-TR. A measure of general cognitive capacity was estimated using the Vocabulary, Similarities, Block Design and Matrix Reasoning subtests of the Wechsler Intelligence Scale for Children (WISC-III) [47] or the Wechsler Adult Intelligence Scale (WAIS-III) [48], for participants aged sixteen and over. A more thorough neuropsychological assessment was also carried out to assess executive function (Wisconsin Card Sorting Test), attention (Continuous Performance Test; Digit Span, WAIS/WISC-III) and memory (Test of Memory and Learning: immediate and delayed recall).

### Imaging data acquisition

Scans were obtained on a 3 Tesla Siemens Magnetom Trio Tim (Siemens Medical Systems, Germany) magnetic resonance scanner at the Centre for Image Diagnosis, Hospital Clínic, Barcelona. Participants were instructed to remain as still as possible for the duration of the scanning session. Soft pads were placed at the sides of their heads in order to help avoid further movement. A high-resolution T1-weighted 3-dimensional (3D) magnetization-prepared rapid sequence was acquired with the following parameters: 240 sagittal slices; TR = 2300 ms; TE = 3.01 ms; slice thickness = 1 mm; inversion time (TI) = 900; FOV = 394x240; matrix size = 256x256; and flip angle = 9°. An 8-minute rs-fMRI sequence was also acquired, prior to which participants were instructed to keep their eyes closed and not fall asleep. Acquisition parameters were as follows: 240 volumes, TR = 2000 ms; TE = 29 ms; matrix size = 480x480; slice thickness = 4 mm, acquisition matrix = 80x80 mm, 32 slices, voxel size 3x3x4 mm<sup>3</sup>.

Following acquisition, images were inspected to exclude participants with macroscopic abnormalities. One BD-offspring was excluded due to ventriculomegalia. rs-fMRI Images were also inspected for excessive head motion during pre-processing, defined as 1.5 mm translation and 1.5 degrees rotation in any of the x, y or z directions. This led to exclusion of 19 participants (6 SZ-offspring, 7 BD-offspring, 6 CC-offspring). The total sample analysed consisted of 27 SZ-offspring, 39 BD-offspring and 40 CC-offspring.

### Statistical analysis

Demographic, clinical and cognitive data were analysed with the Statistical Package for Social Sciences (SPSS v.20) employing repeated measures analyses of variance and chi-square tests. Non-parametric testing and log-transformation of variables were undertaken when assumption of normality was not met (Kolmogorov-Smirnov). Age correlated with performance on immediate and delayed memory tasks as well as with digit span, therefore cognitive measures were regressed for age prior to performing between-group comparisons.

### Image processing and analysis

rs-fMRI data was preprocessed with the Statistical Parametric Mapping software (SPM8), running in Matlab (R2013a), as follows: reorientation of 3D and fMRI images along the anterior and posterior commissural line; realignment with motion correction and inspection of outputs; coregistration of anatomical to functional data; normalization into standard Montreal Neurological Institute (MNI) space [49] and smoothing with an 8 mm FWHM kernel. Images were then subjected to a single spatial ICA, employing the Group ICA fMRI Toolbox (GIFT v3.0a), performed in 3 stages: First, principal component analyses (PCA) was conducted twice: the dataset was first reduced to 30 components, and then was further reduced to 20 components. The first PCA reduction step is at the subject level and the second one at the group level. Subject-level PCA allows preservation of differences between subjects at the same time that it emphasizes the similarities between subjects by projecting data into a common space. This

point enables acquisition of mean data for the subjects and is required to make the data computationally tractable. On the other hand, by conducting group-level PCA, data is further reduced into a set number of components and independent group spatial maps [50]. Second, the Info-max algorithm was used to decompose the reduced dataset into maximally independent component images; and finally, back-reconstruction of components using the Group ICA tool. Components were sorted by spatial correlation with a template of the DMN provided by the GIFT software, as well as with templates for the ECN, BGN, and anterior SN available at [http://findlab.stanford.edu/functional\\_ROIs.html](http://findlab.stanford.edu/functional_ROIs.html) [51]. Components showing the greatest correlation with the templates were exported to SPM8, where one sample t-tests were carried out to determine anatomical regions within each network. Then, ANCOVA was conducted to test the effect of group membership on within network connectivity, with age and gender as covariates. A grey matter mask was obtained from the smoothed, modulated and normalised grey matter images for the whole sample, which was used as an inclusive mask for all second-level analyses. Significant main effects of group were followed-up with pairwise comparisons. Results were interpreted at a voxel-wise threshold of  $p < 0.001$  uncorrected and a cluster-wise threshold of  $p < 0.05$  FWE corrected. Connectivity signal values from clusters showing significant group differences were extracted using a volume-of-interest (VOI) approach in order to examine the relationship between magnitude of connectivity and clinical, cognitive and grey matter volume (GMV) measures.

Computation of GMV within the clusters identified in the above comparisons was undertaken with a customised script running in Matlab. T1 images underwent a unified segmentation followed by smoothing with an 8mm FWHM kernel. In order to adjust for head size, a grey matter ratio was obtained for each subject (GMV of the cluster was divided by the subject's total intracranial volume (TIV), [52]). TIV was computed using the Freesurfer pipeline [53]. ANCOVA was used to determine the effect of group on GMV within clusters identified in the above comparisons, with age and gender as covariates. The relationship between rs-fMRI signal (within the cluster showing between group differences) and clinical, cognitive and volumetric data was assessed using partial correlations controlling for age and gender.

Finally, analyses were repeated excluding offspring with a history of any axis I DSM-IV diagnosis. Confirmatory analyses were also performed to take into account the effect of having a sibling in the sample (5 SZ, 9 BD, and 8 CC families contributed more than one offspring to the study): mixed models were conducted with SPSS, where the mean connectivity values were included as dependent variable, 'sibship' as random effects, and age and gender as fixed effects.

## Results

Out of the final 22 SZ families, 18 parents had a diagnosis of SZ (DSM-IV codes 295.10–90), while 3 parents had a diagnosis of schizoaffective disorder (DSM-IV codes 295.40). Out of the 28 BD families, 18 parents had BD-I (DSM-IV codes 296.40–70), and 7 had BD-II (DSM-IV codes 296.89). All other current and lifetime psychiatric diagnoses of parents (proband parents, co-parents and community control parents) are shown in [Table 1](#). No significant differences in terms of rates of lifetime or current axis I diagnoses were observed between the three groups of parents (SZ, BP, CC;  $\chi^2 = 1.263$ ,  $p = 0.532$ ).

Demographic, clinical, cognitive and neuroimaging data of the offspring are depicted in [Table 2](#). There was no significant effect of group on age, sex or TIV. SZ-offspring had lower parental SES relative to the other groups. SZ had greater lifetime prevalence of attention deficit hyperactivity disorder (ADHD) than CC-offspring. There were no other clinical differences, except for SZ and BD-offspring showing higher SOPS negative scores than CC-offspring. Six participants (5 SZ-offspring and 1 BD-offspring) were receiving treatment with

Table 1. Clinical characteristics of parents.

	Schizophrenia proband parents (N = 19)	Schizophrenia co-parents (N = 17)	Bipolar Disorder proband parents (N = 30)	Bipolar Disorder co-parents (N = 23)	Community Control parents (N = 53)
	Mean (standard deviation) / N (%)				
Age	41.69 (6.16)	46.61 (9.75)	45.14 (5.52)	45.87 (5.51)	45.09 (5.41)
Total lifetime axis I disorders*	7 (36.84%)	10 (58.82%)	11 (36.67%)	9 (39.13%)	19 (35.86%)
Lifetime attention deficit hyperactivity disorders	0	0	1 (3.33%)	0	0
Lifetime mood disorders	2 (10.53%)	4 (23.53%)	5 (16.67%)	2 (8.70%)	3 (5.66%)
Lifetime anxiety disorders	1 (5.26%)	0	3 (10%)	0	3 (5.66%)
Lifetime adjustment disorders	2 (10.53%)	6 (35.29%)	2 (6.67%)	4 (17.39%)	11 (20.75%)
Lifetime substance-related disorders	1 (5.26%)	0	0	2 (8.70%)	0
Lifetime eating disorders	1 (5.26%)	0	0	1 (4.35%)	2 (3.77%)
Total current axis I disorders*	0	6 (35.29%)	6 (20%)	7 (30.43)	9 (16.98%)
Current attention deficit hyperactivity disorders	0	0	2 (6.67%)	0	0
Current mood disorders	0	3 (17.65%)	0	0	0
Current anxiety disorders	0	2 (11.76%)	2 (6.67%)	4 (17.39%)	3 (5.66%)
Current adjustment disorders	0	1 (5.88%)	1 (3.33%)	2 (8.70%)	6 (11.32%)
Current substance-related disorders	0	0	1 (3.33%)	1 (4.35%)	0

\* All axis I-related disorders other than schizophrenia and bipolar disorder are considered.

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psychostimulants for treatment of ADHD at the time of scanning; no other participant had received any other form of psychiatric medication. CC-offspring had higher IQ relative to SZ-offspring. No significant differences were seen in any other cognitive domain. No differences in peak translation or rotation motion parameters were observed between groups.

### Independent component analysis

Spatial maps for each network are described in [Table 3](#).

An effect of group membership was detected for the BGN ( $F = 13.07$ ,  $p_{FWE} = 0.019$ ,  $k = 55$ , MNI coordinates  $x,y,z [-9,23,-2]$ ). Pairwise analyses showed that this finding was driven by the SZ-offspring versus CC-offspring comparison: SZ-offspring showed reduced connectivity in the left caudate nucleus and anterior cingulate, extending to the left olfactory cortex ( $t = 4.45$ ,  $p_{FWE} = 0.012$ ,  $k = 80$ , MNI  $[[ -9,23,-2]]$ ). This pairwise comparison survived Bonferroni correction ( $p$ -value threshold  $0.05/3 = 0.017$ ). There were no differences between BD-offspring and CC-offspring, or between SZ-offspring and BD-offspring. [Fig 1A](#) illustrates the effect of group on connectivity within the BGN, including mean signal intensity at the left caudate ([Fig 1B](#)). When IQ was entered in the model, results remained unchanged (group effect,  $F = 10.97$ ,  $p_{FWE} = 0.022$ ,  $k = 53$ , MNI  $[[ -9,23,1]]$ ; pairwise comparison SZ-offspring < CC-offspring  $t = 4.21$ ,  $p_{FWE} = 0.004$ ,  $k = 100$ , MNI  $[[ -3,17,1]]$ , left olfactory cortex extending to the caudate nuclei). A group effect was also detected in the right ECN, albeit at an uncorrected threshold ( $F = 10.96$ ,  $p_{uncorrected} = 0.026$ ,  $k = 23$ , MNI  $[[ 36,-79,31]]$ ); this was driven by increased

**Table 2. Socio-demographic, clinical and cognitive characteristics of the sample.**

	Schizophrenia Offspring (N = 27)	Bipolar Disorder Offspring (N = 39)	Community Control Offspring (N = 40)	Statistic	P value	Significant pair-wise comparisons, Bonferroni corrected p (0.05/3 = 0.017)
	Mean (standard deviation) / N (%)					
<b>Age</b>	11.96 (3.41)	13.87 (3.49)	13.45 (3.76)	4.21 <sup>a</sup>	0.122	
<b>Sex (female)</b>	13 (48.15%)	22 (56.41%)	24 (60%)	0.932 <sup>b</sup>	0.628	
<b>Socio-economic status<sup>1</sup></b>	38.56 (12.17)	47.05 (13.11)	50.23 (10.86)	12.05 <sup>a</sup>	0.002	CC-offspring>SZ-offspring p<0.0001 BP-offspring>SZ-offspring p = 0.014
<b>Lifetime attention deficit hyperactivity disorders</b>	9 (33.33%)	6 (15.38%)	1 (2.5%)	11.962 <sup>b</sup>	0.003	SZ-offspring > CC-offspring (p<0.0001);
<b>Lifetime mood disorders<sup>2</sup></b>	2 (7.41%)	1 (2.56%)	2 (5%)	0.844 <sup>b</sup>	0.656	
<b>Lifetime anxiety disorders<sup>3</sup></b>	2 (7.41%)	5 (12.82%)	0	5.30 <sup>b</sup>	0.071	
<b>Lifetime disruptive behaviour disorders<sup>4</sup></b>	1 (3.70%)	1 (2.56%)	1 (2.5%)	0.101 <sup>b</sup>	0.951	
<b>YMRS<sup>5</sup></b>	2.08 (3.43)	1.32 (1.85)	0.94 (1.72)	1.555 <sup>a</sup>	0.459	
<b>HDRS<sup>6</sup></b>	0.8 (1.22)	2.23 (4.33)	0.50 (1.25)	3.422 <sup>a</sup>	0.181	
<b>SOPS-P<sup>7</sup></b>	1.36 (2.18)	1.10 (2.60)	0.61 (1.57)	2.824 <sup>a</sup>	0.244	
<b>SOPS-N<sup>8</sup></b>	1.00 (1.57)	1.61 (3.40)	0.31 (1.06)	8.185 <sup>a</sup>	0.017	BD-offspring > CC-offspring (p = 0.016); SZ-offspring > CC-offspring (p = 0.006)
<b>Maximum translation movement (mm)</b>	0.62 (0.38)	0.61 (0.38)	0.53 (0.27)	0.779 <sup>a</sup>	0.678	
<b>Maximum rotation movement (degrees)</b>	0.57 (0.44)	0.50 (0.36)	0.45 (0.34)	1.097 <sup>a</sup>	0.578	
<b>Total intracranial volume (cc)</b>	1501.03 (153.79)	1541.12 (143.64)	1529.49 (168.45)	2.176 <sup>a</sup>	0.337	
<b>Total Grey matter volume (cc)</b>	715.14 (69.50)	713.39 (58.19)	718.43 (72.02)	0.057 <sup>c</sup>	0.944	
<b>General Cognitive Capacity<sup>9</sup></b>	101.30 (14.77)	108.26 (11.80)	110.60 (12.32)	4.40 <sup>c</sup>	0.015	CC-offspring > SZ-offspring (p = 0.013)
<b>WCST<sup>10</sup>-correct answers</b>	70.14 (7.61)	68.38 (9.77)	71.67 (9.13)	0.863 <sup>c</sup>	0.426	
<b>WCST-complete categories</b>	5.33 (1.68)	5.96 (0.20)	5.84 (0.50)	2.724 <sup>c</sup>	0.072	
<b>TOMAL<sup>11</sup>-immediate recall</b>	76.09 (8.78)	81.85 (8.66)	80.67 (8.24)	0.7 <sup>c</sup>	0.5	
<b>TOMAL-delayed recall</b>	9.86 (2.01)	10.61 (1.50)	10.59 (1.46)	0.623 <sup>c</sup>	0.539	
<b>CPT<sup>12</sup>-reaction time</b>	51.23 (9.66)	51.57 (11.65)	46.41 (9.20)	2.566 <sup>c</sup>	0.083	
<b>Digit span</b>	14.05 (2.73)	16.46 (3.31)	16.03 (2.80)	2.186 <sup>c</sup>	0.119	

<sup>1</sup>Hollingshead Index.

<sup>2</sup>Mood disorders: dysthymia and adjustment disorder with depressed mood.

<sup>3</sup>Anxiety disorders: simple phobia, generalized anxiety disorder and obsessive-compulsive disorder.

<sup>4</sup>Disruptive behaviour disorders: oppositional defiant and conduct disorder.

<sup>5</sup>Young Mania Rating Scale;

<sup>6</sup>Hamilton Depression Rating Scale;

<sup>7</sup>Scale of Prodromal Symptoms: positive symptoms;

<sup>8</sup>Scale of Prodromal Symptoms: negative symptoms;

<sup>9</sup>Wechsler Intelligence Scale for Children-III/Wechsler Adult Intelligence Scale-III

<sup>10</sup>Wisconsin Card Sorting test,

<sup>11</sup>Test of Memory And Learning,

<sup>12</sup>Continuous Performance Test.

<sup>a</sup>Kruskal-Wallis;

<sup>b</sup>Chi-square;

<sup>c</sup>ANOVA. Pairwise comparisons were corrected for Bonferroni, setting the p value threshold at 0.017 (alpha value divided into three main comparisons).

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Table 3. Resting-state components.

Resting State Networks	Correlation (r) with spatial template for the whole sample	Correlation (r) with spatial template for offspring without a history of psychiatric disorders	Main anatomical locations
Default Mode Network	0.59351	0.52258	Left: Precentral and paracentral lobule, superior frontal, inferior occipital cortices, inferior parietal lobe and posterior cingulate. Right: Middle/inferior/superior frontal cortex, precuneus, middle occipital, inferior/superior parietal and middle temporal cortices.
Basal Ganglia Network	0.4039	0.41902	Pallidum, anterior cingulate, thalami, putamen, caudate, right posterior cingulate, right superior frontal and right middle temporal cortices.
Left Executive Control Network	0.42065	0.48866	Left: orbitofrontal, superior/inferior/middle/medial frontal, inferior parietal and inferior temporal cortices. Right: supramarginal gyrus and middle/superior occipital cortex.
Right Executive Control Network	0.4239	0.42226	Left: precuneus, paracentral lobule and posterior cingulate. Right: superior/middle/inferior/medial frontal, precentral, inferior parietal and middle temporal cortices, fusiform gyrus, precuneus, and insula.
Anterior Salience Network	0.56265	0.39225	Left: precentral cortex, amygdala, anterior/middle cingulate, paracentral lobule, medial/superior/middle orbital frontal cortex, and globus pallidum. Right: superior/middle/inferior frontal cortices, cerebellum, inferior temporal cortex and inferior parietal lobe.

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connectivity in BD-offspring relative to the other groups, particularly SZ-offspring ( $t = 4.68$ ,  $p_{FWE} = 0.035$ ,  $k = 61$ , MNI [36,-79,31]). No significant group differences were seen for the DMN or SN.

Given that volumetric reduction of the caudate nucleus has been associated with ADHD [54] and that treatment with psychostimulants may modulate caudate activity [55], we conducted a second-level analysis excluding 9 SZ-offspring, 6 BD-offspring and 1 CC-offspring with ADHD, among which were the six subjects receiving psychotropic medications at the time of scanning. Results remained near significant for the same cluster ( $t = 4.60$ ,  $p_{FWE} = 0.05$ ,  $k = 54$ , MNI [-9,26,-5]). Analyses excluding subjects with lifetime history of axis I disorders did not yield any significant changes to the group differences within the BGN, albeit at an

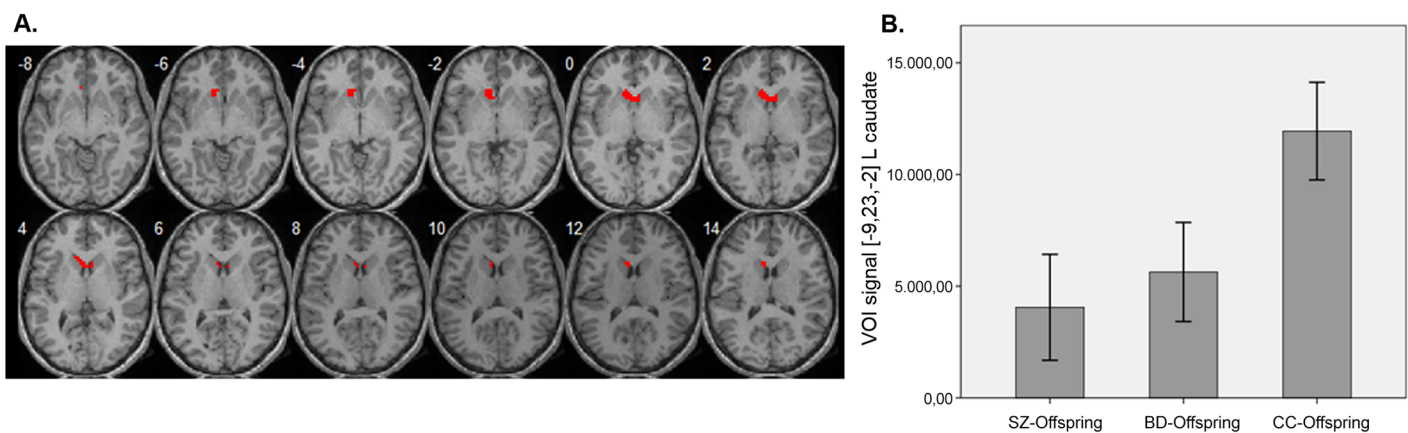
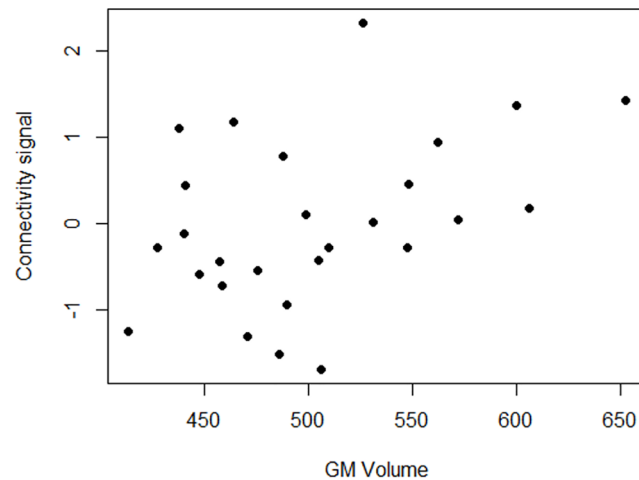


Fig 1. A. Cluster showing group differences within the Basal Ganglia Network overlaid on a normalised 3D image. B. Mean signal intensity for each group within the global maxima in the BGN. Error bars represent the 95% confidence interval.

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**Fig 2. Partial regression plot depicting correlation between VOI signal values and grey matter volume in the left caudate (SZ-offspring).**

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uncorrected statistical threshold (SZ-offspring < CC-offspring:  $t = 4.82$ ,  $p_{\text{unc}} = 0.012$ ,  $k = 43$ , MNI  $[-9, 26, -5]$ ). Analyses taking into account the effect of sibship in this same region within the BGN confirmed the abovementioned results ( $F = 11.87$ ,  $p < 0.0001$ ; Bonferroni correction).

### Relationship between RSN and brain structural, clinical and cognitive variables

GMV of the cluster showing significant between group differences in the BGN was measured for each participant. No differences in GMV/TIV ratio were seen between groups ( $F = 0.36$ ,  $p = 0.699$ ). Correlation analyses were also conducted applying Bonferroni correction ( $p = 0.05$  divided by the number of structural, clinical and cognitive variables (12), yielded a threshold of statistical significance at  $p < 0.004$ ). There was a positive correlation between rs-fMRI signal and regional GMV in SZ-offspring only ( $R^2 = 0.598$ ,  $p = 0.032$ , unstandardized coefficient  $\beta = 37.54$ , standard error = 16.47, see Fig 2). No significant associations were observed between the rs-fMRI signal and clinical/cognitive variables.

### Discussion

This is, to the best of our knowledge, the first study to directly compare rs-fMRI in child and adolescent offspring of patients with SZ and BD. We found reduced left BGN connectivity in SZ-offspring relative to CC-offspring that correlated with GMV in the left caudate, and no differences in connectivity between BD-offspring and CC-offspring.

Hypoconnectivity in the left BGN in SZ-offspring involved the left caudate nucleus, the anterior cingulate and ventromedial prefrontal cortex. These findings remained, at an uncorrected threshold, after excluding offspring with pre-existing lifetime psychiatric diagnoses. Decreased resting-state corticostriatal connectivity has been previously reported in siblings and parents of patients with psychotic disorders [31, 11]. The present study expands these findings and demonstrates that BGN hypo-connectivity may be a robust correlate of familial risk for SZ, regardless of age. Unlike Fornito and colleagues, we did not confirm an association between BGN connectivity and clinical and cognitive symptoms. These authors found a correlation between fronto-striatal connectivity and positive and negative symptoms in patients with first-episode psychosis [31], but they failed to assess this relationship in their group of first degree

relatives. Our sample involved young offspring of BD and SZ, none of whom had a diagnosis of psychosis; hence why we decided to focus on prodromal symptoms. The correlation between intrinsic connectivity and symptomatology may thus emerge as the sample grows older and approaches the peak age of onset of the disease; the association between neural signal and clinical symptoms being too subtle to be detected at this early stage. On the other hand, we observed a positive correlation between BGN connectivity signal and GMV in the left caudate, restricted to SZ-offspring, indicating that lower connectivity is associated with smaller GMV in this region in SZ-offspring, despite the absence of case-control differences in volume. In a sample of adolescent SZ-offspring, Tandon and colleagues observed reductions in N-acetyl aspartate in the caudate, thalamus and anterior cingulate gyrus and increases in glutamate + glutamine in the caudate and thalamus, which correlated with respective GMV [56]. The authors postulated that these findings could reflect abnormal glutamatergic–dopaminergic interactions in these regions, linking with the large body of research supporting abnormal striatal dopamine transmission in unaffected adult relatives of patients with SZ [57] and adults at clinical high risk for psychosis [58].

We did not observe differences in BGN connectivity between BD-offspring and CC-offspring. Khadka and colleagues, in an adult sample, also demonstrated that decreased striatal connectivity was specific to relatives of SZ, although they observed disruption in connectivity of the thalamus in both SZ and BD relatives [11]. Longitudinal follow-up of our sample will allow to confirm whether such abnormalities emerge with increasing age, or whether they remain unrelated to familial risk.

We also found evidence indicative of greater connectivity in BD-offspring in the right ECN, which was more prominent in their comparison to SZ-offspring. The ECN network overlaps with regions frequently activated during executive function tasks such as working memory [59]. A study in young SZ-offspring [60] found reduced fronto-parietal activation during a working memory task, which suggests that abnormalities in the ECN may be more reliably present when the network is actively involved in a task. However, this finding may also be reflective of compensatory network connectivity in BD-offspring. This interpretation has also been suggested by Singh and colleagues who observed increased ECN connectivity in child and adolescent BD-offspring [30]. Nevertheless, given that these results were uncorrected for multiple comparisons conclusions remain tentative.

Contrary to previous studies [27], we found no differences of connectivity in the DMN. Of note, our DMN component did not include the medial prefrontal cortex, which we hypothesize may be due to the young age of the sample. The age-related re-organization of the DMN involves increased functional connectivity, particularly in the medial prefrontal cortex [61]. Abnormalities related to risk of SZ and BD in this network may thus emerge as this sample grows into adulthood.

The SN did not yield significant results in any of the contrasts studied. Some functional alterations have been previously reported in patients with SZ [15], and abnormal structural covariance within this network has been reported in prodromal subjects who later transitioned to psychosis [62]. It is therefore possible that such dysfunction may be specific to those individuals who will later develop psychosis, and therefore not detectable at the group level. Furthermore, some studies have considered subcortical structures as a part of this network [15, 62], while in our study we have differentiated between cortico-subcortical and a fronto-insular network, which may have contributed to the lack of results in our salience component.

This study has a number of limitations. Given its cross-sectional design, we are unable to comment on the development of RSN in high-risk offspring. We included offspring receiving psychotropic medication or with different diagnoses in order to capture the clinical complexity of high-risk samples [63], although this did not influence the results. The main strength of our

study is the direct comparison of SZ-offspring and BD-offspring during youth, which coincides with the age at which the incidence of both disorders begins to rise [64]. It has been suggested that research focused on adult samples may be missing important ethiopathogenic processes which take place earlier during development [65].

In conclusion, our findings point to a measurable pattern of brain dysconnectivity across RSN in child and adolescent offspring of SZ, while no functional connectivity differences were observed in BD-offspring relative to CC-offspring. Follow-up of the current sample will allow tracking whether the current changes are predictive of transition to psychosis.

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## Author Contributions

Conceived and designed the experiments: GS JCF CSP. Performed the experiments: EdS VSG SR IB MPF NB. Analyzed the data: CSP GS AC. Contributed reagents/materials/analysis tools: NB JCF GS. Wrote the paper: CSP GS SF JCF EdS.

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