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Genetic and Structural Brain Correlates of Cognitive Subtypes Across Youth at Family Risk for Schizophrenia and Bipolar Disorder

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Abstract:	Background : Cognitive impairment is an important feature of Schizophrenia (SZ) and Bipolar Disorder (BP) with severity across the two disorders characterized by significant heterogeneity. We clustered youth at family risk for SZ and BP based on cognitive function and examined the clinical, genetic and brain imaging correlates of cluster membership. Methods : 160 participants, 32 offspring of patients with SZ (SZO), 59 offspring of patients with BP (BPO) and 69 offspring of healthy control parents (HCO) underwent clinical and cognitive assessments, genotyping and structural MRI. K-means clustering was used to group family risk participants based on cognitive measures. Clusters were compared in terms of cortical and subcortical brain measures as well as polygenic risk scores for SZ (PRS-SZ), for BP (PRS-BP) and for cognitive function (PRS-COG). Results : Participants were grouped in three clusters, with intact, intermediate and impaired cognitive performance. The intermediate and impaired clusters had lower total brain surface area compared to the intact cluster, with prominent localization in frontal and temporal cortices. No between-cluster differences were identified in cortical thickness and subcortical brain volumes. The impaired cluster also had poorer psychosocial functioning and worse PRS-COG compared to the other two clusters and to HCO, while there was no significant between-cluster difference in terms of PRS-SZ and PRS-BP. PRS-COG predicted psychosocial functioning, yet this effect didn't appear to be mediated by an effect of PRS-COG on brain area. Conclusions : Stratification based on cognition may help to elucidate the biological underpinnings of cognitive heterogeneity across SZ and BP risk.

Genetic and Structural Brain Correlates of Cognitive Subtypes Across Youth at
Family Risk for Schizophrenia and Bipolar Disorder
RH = Neurobiology of Cognition in Psychosis Risk

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Clinical Guidance
Supplemental Material

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Abstract

Objective: Cognitive impairment is an important feature of Schizophrenia (SZ) and Bipolar Disorder (BP) with severity across the two disorders characterized by significant heterogeneity. We clustered youth at family risk for SZ and BP based on cognitive function and examined the clinical, genetic and brain imaging correlates of cluster membership.

Method: 160 participants, 32 offspring of patients with SZ (SZO), 59 offspring of patients with BP (BPO) and 69 offspring of healthy control parents (HCO) underwent clinical and cognitive assessments, genotyping and structural MRI. K-means clustering was used to group family risk participants based on cognitive measures. Clusters were compared in terms of cortical and subcortical brain measures as well as polygenic risk scores for SZ (PRS-SZ), for BP (PRS-BP) and for cognitive function (PRS-COG).

Results: Participants were grouped in three clusters, with intact, intermediate and impaired cognitive performance. The intermediate and impaired clusters had lower total brain surface area compared to the intact cluster, with prominent localization in frontal and temporal cortices. No between-cluster differences were identified in cortical thickness and subcortical brain volumes. The impaired cluster also had poorer psychosocial functioning and worse PRS-COG compared to the other two clusters and to HCO, while there was no significant between-cluster difference in terms of PRS-SZ and PRS-BP. PRS-COG predicted psychosocial functioning, yet this effect didn't appear to be mediated by an effect of PRS-COG on brain area.

Conclusion: Stratification based on cognition may help to elucidate the biological underpinnings of cognitive heterogeneity across SZ and BP risk.

Key words: psychosis risk, children, MRI clusters

Introduction

Schizophrenia (SZ) and Bipolar Disorder (BP) share clinical ¹, genetic ² and structural brain features ³, but the same domains are also characterized by significant differences with disease specific abnormalities ^{2,3}. Both disorders include cognitive impairment as a key symptom dimension, considered to be an important determinant of psychosocial functioning ⁴. Cognitive abnormalities are qualitatively similar across the two diagnostic groups, but overall severity is milder in BP compared to SZ ⁵. The Research Domain Criteria approach suggests that current diagnostic categories might not provide the most reliable framework to elucidate pathophysiological mechanisms ⁶. Cognition was thus proposed amongst a number of potential transdiagnostic dimensions to be used as intermediate phenotypes. Intermediate phenotypes are considered to be less complex compared to clinical constructs such as SZ and BP, and more proximal to the underlying pathophysiology ⁷. On this basis a few studies employed a cross-diagnostic approach and clustered patients based on cognitive function rather than SZ or BP diagnosis ⁸⁻¹⁰. They consistently identified a group characterized by spared cognition, one with severe cognitive impairments, and one or more intermediate groups, with milder or selective deficits. Both diagnostic groups were represented in each of the clusters, though patients with SZ were more frequently identified in the severely impaired group. Cognitive deficits of a similar magnitude can thus be observed in both SZ and BP, and milder overall severity in BP appears to reflect a smaller proportion of severe impairment cases compared to SZ. A few studies then sought to examine the neuroanatomical correlates of cognitive subtypes, either within SZ ¹¹⁻¹³ or across SZ and BP ^{14,15}. One reported no mapping of

1 brain morphology onto cognition ¹⁴, yet the majority identified grey matter volume
2 abnormalities in the severely impaired group compared to the more preserved groups
3 and to healthy controls (HC) ^{11-13,15}. Differences were observed in global brain
4 measures, with significant reductions especially in frontal and temporal cortices <sup>11-
5 13,15</sup>, as well as subcortical regions ^{12,13,15}, particularly the hippocampus ^{12,15}.

11 SZ, BP and cognition have reported heritability estimates around 0.6, 0.8 ² and 0.5 ¹⁶,
12 respectively. Several population-based genome-wide association studies (GWAS)
13 have examined their genomic correlates and potential overlaps ^{17,18}. Most identified
14 negative correlations between SZ and cognitive function but no significant
15 correlations between cognition and BP ^{17,18}. A recent study though, revealed extensive
16 genetic overlaps between SZ, BP and cognitive function, suggesting that a significant
17 proportion of the genetic architecture underlying genetic risk for SZ and BP also has
18 an influence on cognition ¹⁹. However, when employing polygenic risk scores (PRS),
19 which aggregate the effects of thousands of common genetic variants on particular
20 clinical or behavioral phenotypes, the analysis of the genetic underpinnings of
21 cognitive function has produced mixed results ^{20,21}. Some evidence suggested a
22 negative correlation between PRS for SZ (PRS-SZ) and cognitive function ²⁰, yet, in
23 other instances, no relationship was identified ²¹. A higher PRS for BP (PRS-BP) was
24 also associated with poorer cognition, but this was mostly driven by single nucleotide
25 polymorphisms (SNPs) that are shared between PRS-BP and PRS-SZ ²². The largest
26 study to date, however, reported cognition in SZ to be more strongly associated with
27 polygenic risk scores that index cognitive traits in the general population, such as PRS
28 for cognition (PRS-COG) or for educational attainment (PRS-EA) rather than PRS-
29 SZ ²¹.

Cognitive heterogeneity in both SZ and BP can be observed prior to illness onset and is considered to reflect heterogeneous neurodevelopmental trajectories⁵. Examining cognitive function in populations at risk for both disorders is therefore critical for the understanding of etiopathological mechanisms. In a recent study we, for the first time, employed a transdiagnostic risk approach and clustered youth at familial risk for SZ and BP based on cognitive performance rather than parental diagnosis²³. Similarly to what has been observed after illness onset⁸⁻¹⁰ we identified three cognitive clusters, one with moderate impairments (*impaired* cluster), one with spared cognition (*intact* cluster) and one with mild impairments, intermediate between the other two (*intermediate* cluster). Both the offspring of patients with SZ (SZO) and the offspring of patients with BP (BPO) were identified in each of the clusters, yet not evenly. A larger proportion of SZO were members of the impaired cluster but there was also a BPO representation. The study confirmed that more severe deficits are not specific to SZO but rather less frequent in BPO.

In the present study we sought to examine the imaging and genetic correlates of cluster membership. To this end, we included all participants of the previous study that had also undergone genotyping and structural MRI. Groups were compared in terms of global and regional measures of cortical thickness and surface area as well as subcortical brain volumes. We hypothesized that participants in the impaired cluster would have reduced cortical thickness and surface area compared to the intact cluster and to healthy control offspring (HCO), particularly in frontal and temporal regions, and smaller hippocampi. We also compared groups in terms of PRS for each of the two disorders and for cognition and hypothesized that participants in the impaired cluster would have more disadvantageous PRS profiles, with higher diagnostic PRSs and lower PRS-COG. Finally, we sought to examine the relationship between

1 biological and clinical variables. We assumed that genes would predict behavior and
2 that part of such relationship would be mediated by an effect of the genes on the
3 brain. In particular, since our participants have yet to reach the mean age of onset for
4 the parental disorders, we focused on psychosocial functioning, also in light of the
5 important relationship between cognition and functioning outcomes in both SZ and
6 BP ⁴. We thus examined the relationship between genetic, imaging and psychosocial
7 functioning measures. We hypothesized that, regardless of cluster membership, more
8 disadvantaged PRSs would be associated with poorer functioning and that part of
9 this effect would be mediated by a genetic effect on brain structure.
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24 **Method**

25 Participants

26 The study included 160 participants aged between 6 and 17 years, of which 91 were at
27 familial risk for SZ or BP and 69 were offspring of healthy control parents (HCO).
28 Family risk participants (32 SZO and 59 BPO) were recruited liaising with adult
29 psychiatric services at the Hospital Clínic in Barcelona and the Hospital Gregorio
30 Marañón in Madrid. They were included if one of their parents was diagnosed with
31 SZ or BP. Control participants were recruited through advertisement in community
32 services of the same geographical area. They were excluded if they had first or second
33 degree family history of either SZ or BP and if they met criteria for any psychiatric
34 diagnosis at the time of assessment, including sub-threshold psychotic symptoms
35 meeting criteria for an At Risk Mental State for psychosis. Additional exclusion
36 criteria for the whole sample were intellectual disability, history of significant head
37 injury or current medical or neurological condition and non-European ancestry.
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Participants were a subsample of those examined in a previously published study²³ in which k-means clustering was employed to group family risk participants based on measures of attention, processing speed, working memory, verbal memory, visual memory and executive function. Results supported a three-cluster solution with an intact, an intermediate and an impaired group. Of the above-mentioned sample, participants were included in the present study if they had also undergone structural MRI and provided blood or saliva for the extraction of genetic information (Supplement 1, available online). Participants were included if both imaging and genetic data met quality control procedures described in the respective analysis sections.

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 2013. Written informed consent was obtained from one of the parents, having the other parent been informed, together with written assent from the participant if aged 12 and above.

Clinical and functioning assessment

Trained psychiatrists assessed both parents using the Spanish version of the Structured Clinical Interview for DSM-IV Disorders (SCID-I)²⁴. Trained child psychiatrists and psychologists, blind to parental diagnosis, conducted the children's assessment using the Spanish version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime version (K-SADS-PL)²⁵, administered separately to parents and children. Other clinical measures included the Clinical Global Impression (CGI)²⁶ and the Scale of Prodromal Symptoms (SOPS)²⁷. The Children's Global Assessment Scale (CGAS)²⁸ was used to assess

1 psychosocial functioning, the Hollingshead-Redlich scale to assess socioeconomic
2 status (SES) ²⁹ and the Spanish version of the Wechsler Intelligence Scale for
3 Children-Fourth Edition (WISC-IV) ³⁰ for general intelligence (IQ).
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9 MRI data acquisition and processing

10 Structural T1-weighted brain magnetic resonance imaging data were acquired using
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12 two different MRI scanners: a 3T Siemens Magnetom TrioTim scanner at the
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14 Hospital Clínic in Barcelona and a 1.5 T Philips Intera scanner at the Hospital
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16 Gregorio Marañón in Madrid. Scanning protocols were described before ³¹ and are
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18 summarized in Table S1, available online. FreeSurfer v7.2.0 was used for cortical
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20 reconstruction and volumetric segmentation. All scans were visually inspected by two
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22 trained raters followed by quality control procedures implemented according to the
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24 ENIGMA protocol (<http://enigma.ini.usc.edu/protocols/imaging-protocols/>). Global
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26 brain measures, regional cortical thickness and surface area as well as subcortical
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28 volumes were extracted from individual images ^{32,33} (Supplement 2, available online).
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30 Combining imaging data across sites introduces non-biological sources of variation
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32 derived from the use of different hardware and scanning protocols ³⁴. To adjust for
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34 site we therefore employed the ComBat batch adjustment method, a harmonization
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36 technique that reduces scan related heterogeneity whilst preserving biological
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38 associations within the data ³⁴ and that has been shown to outperform other methods
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40 for removing the effect of site ³⁵.
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53 Genetic data processing

54 Genotyping data were submitted to the Michigan Imputation Server ³⁶ employing the
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56 standard Minimac4 software pipeline and setting a European Population reference
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1 from build GRCh37/hg19 and Eagle v2.4 phasing. Three GWAS summary results
2 were employed as reference for PRS calculations, for PRS-SZ (69,369 cases and
3 236,642 controls)³⁷, for PRS-BP (20352 cases and 31358 controls)¹⁸ and for PRS-
4 COG (257841 individuals)³⁸ respectively. Duplicated and unknown strand GWAS
5 summary SNPs were excluded.
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11 Quality control was performed with PLINK v1.07³⁹. Inclusion criteria for SNPs were
12 minor allele frequency (MAF) > 0.1, Hardy-Weinberg equilibrium $p > 10^{-6}$, marker
13 missingness < 0.01 and imputation INFO > 0.8. Pruning was done using a
14 window/step size of 200/50 kb and $r^2 > 0.25$. Sample quality control included
15 individuals with heterozygosity values within three standard deviations (SD) from the
16 mean, a missingness rate < 0.01, matching chromosomal and database-labeled sex and
17 self-reported European ancestry. PRS were constructed using the PRSice-2 v2.3.3
18 software⁴⁰ using the odds ratio or beta values of SNPs in the GWAS reference data
19 that had $p < 0.05$. Clumping was set at 250 kb and $r^2 > 0.1$.
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36 Statistical Analyses

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38 Statistical analyses were conducted using IBM SPSS Statistics version 25.
39 Demographic and clinical variables were analyzed with one-way analyses of variance
40 or chi-square tests. For global brain measures we performed between group
41 comparisons employing linear mixed models and reported adjusted means. We took
42 into account sex, age, and total intracranial volume as fixed effects, and family
43 relatedness as random effect. For regional brain measures laterality was included as a
44 further fixed factor in the analysis. For all outcomes linear model assumptions were
45 assessed plotting fitted values and residuals. False discovery rate (FDR) ($q < 0.05$)
46 thresholding was used to control for multiple comparisons for global brain measures,
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1 regional cortical thickness, regional cortical surface area, and subcortical volumes
2 respectively, followed by pairwise post-hoc comparisons. PRS scores were
3 standardized to z-scores with mean 0 and SD of 1 employing data for the whole
4 sample. For each PRS analysis we performed between group comparisons employing
5 linear mixed models controlling for the effects of age, sex, and family, followed by
6 Bonferroni corrected post-hoc pairwise comparisons. Finally, we used R 3.6.1
7 software to perform a mediation analysis ⁴¹ in order to assess the relationship between
8 genetic, imaging and psychosocial functioning measures. A mediated effect occurs
9 when the independent variable's effect on the dependent variable (direct effect) is
10 mediated by another variable (indirect effect). We tested the significance of direct and
11 indirect effects using bootstrapping procedures with 1000 bootstrap samples.
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28 **Results**

29 **Demographic, cognitive and clinical variables**

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31 Participants were a subsample of those included in a previous study ²³, (Supplement 3
32 and Table S2, available online), selected based on imaging and genetic data
33 availability as well as quality control thresholding for both data types, with no
34 significant demographic differences compared to the original sample (Table S3,
35 available online). There were 34 participants in the intact cluster, 40 in the
36 intermediate and 17 in the impaired, with no significant between-cluster difference in
37 the proportion of participants excluded (Table S2, available online).
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53 Parental diagnosis by cluster

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55 Both parental diagnoses were represented in each of the clusters yet in different
56 proportions ($\chi^2=8.942$, $p=0.011$): 44.1% of BPO were in the intact group, 42.4% in
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the intermediate and 13.6% in the impaired, while 25% of SZO were in the intact group, 46.9% in the intermediate and 28.1% in the impaired.

Demographic and clinical characteristics by cluster

Groups did not significantly differ in terms of age but they differed in terms of sex, with a larger proportion of males in the impaired cluster (Table 1). Like in the original sample there was a main effect of cluster for SOPS disorganized subscale but no significant between-cluster difference for any of the other SOPS subscales and for the total score, while there was a main effect of cluster for both CGI and CGAS, with significantly worse scores in the impaired cluster compared to the other two (Table 1). There was also a main effect of group for socioeconomic status with significantly lower values in the impaired cluster compared to the intact and to HCO. As expected the groups significantly differed in terms of IQ (Table 1) and there was a main effect of cluster for all the examined cognitive domains, with between-cluster differences overlapping with those observed in the original sample (Supplement 4 and Table S4, available online). The clusters did not differ in terms of pharmacological treatment (Supplement S5 and Table S5, available online). The prevalence of tobacco, alcohol, and cannabis use was negligible in the whole sample and there wasn't any significant between-group difference (Table S6, available online). None of the participants used any other substances. There was no significant difference between the groups in terms of recruitment center ($\chi^2=0.163$, $p=0.922$) (Supplement 6 and Table S7, available online) or based on whether they had provided blood or saliva for genotyping ($\chi^2=1.314$, $p=0.518$).

Brain Imaging Results

There was no main effect of group in terms of total intracranial volume (ICV) or mean cortical thickness, while there was a significant main effect of group for total surface area (Table 2).

Pairwise post-hoc comparisons revealed that the intermediate and the impaired cluster had significantly smaller total surface area compared to the intact (Table 2). The intermediate cluster also had significantly smaller surface area compared to HCO.

When examining cortical regions, we identified no difference in terms of cortical thickness in any of the areas examined (Table S8, available online) while, for surface area, there was a main effect of group for temporal and frontal cortices (Table 2).

Pairwise post-hoc comparisons revealed that the intact cluster had larger temporal surface area compared to the other two clusters but also to HCO. Similarly, the intact cluster had larger frontal area compared to both the intermediate and the intact cluster, though the latter difference was only observed at trend level. We identified no significant between-group differences in any of the subcortical volumes (Table S9, available online).

Genetic results

Participants were compared in terms of PRS-SZ, PRS-BP, and PRS-COG, calculated using a 0.05 threshold uncorrected (Tab 3).

We identified a significant between-group difference for PRS-COG, while there was no difference for PRS-SZ or PRS-BP. Post hoc comparisons revealed that PRS-COG was lower in the impaired cluster compared to the other two and also compared to HCO (Figure 1), though the comparison with the intact cluster was only significant at trend level (Table 3).

Mediation analysis

We then sought to perform a mediation analysis to examine the relationship between genetic, imaging and psychosocial functioning variables. To do so we selected measures for which we had identified significant between-group differences, as we assumed that these would be more closely related to cognitive heterogeneity compared to variables for which no mapping onto cognition was identified. We therefore employed PRS-COG as independent variable (IV), CGAS as dependent variable (DV), and as mediator we employed total surface area, which was highly correlated with the other findings in temporal and frontal regions (Figure 2).

We first tested the total effect, hence the effect of the IV on the DV and found a significant positive relationship between PRS-COG and CGAS ($p=0.017$). To establish any mediation the IV must significantly affect the proposed mediator. We therefore tested whether there was an influence of PRS-COG on total surface area and found no significant relationship (Supplement 7 and Table S10, available online). We therefore could not detect any mediated effect of PRS-COG on CGAS via total surface area.

Discussion

We examined a sample of children and adolescents at familial risk for SZ and BP in order to investigate the imaging and genetic underpinnings of cognitive heterogeneity across family risk. We had previously clustered participants based on cognitive performance rather than parental diagnosis and identified three performance groups: intact, intermediate and impaired ²³.

1 In line with our first hypothesis the groups differed in terms of brain structure.
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3 Participants in the intermediate and impaired cluster had significantly reduced total
4
5 surface area compared to the intact cluster. The former also had reduced total surface
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7 area compared to HCO. When examining regional differences we observed that
8
9 global findings reflected significant differences in frontal and temporal surfaces. In
10
11 temporal regions participants from the intact cluster had larger surface area not only
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13 compared to the other two clusters but also to HCO. The latter finding suggests that
14
15 larger surface area, particularly in temporal cortices, might confer a degree of
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17 cognitive protection to participants of the intact group. We observed no significant
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19 differences in total ICV, global or regional measures of cortical thickness and
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21 subcortical volumes.
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26 Heterogeneity in terms of cognitive dysfunction after illness onset is considered to
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28 reflect different underlying disease trajectories. A few studies have therefore
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30 attempted to group patients based on the putative timeframe of its emergence,
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32 retrospectively assessing cognitive pathways either within SZ ^{11,12} or across SZ and
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34 BP ¹⁵. Current and estimated premorbid IQ were used to group patients into those
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36 with *preserved* cognition, those whose cognition *deteriorated* after a having displayed
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38 no premorbid deficits and those who were *compromised* both at the time of the
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40 assessment and prior to illness onset. The only study employing this approach across
41
42 SZ and BP reported no grey matter volume differences between preserved patients
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44 and HC, while impaired patients showed reduced grey matter volumes in frontal,
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46 temporal and occipital cortices, as well as in the thalamus, amygdala and
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48 hippocampus ¹⁵. This study assessed premorbid cognitive function retrospectively,
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50 hence our findings in family risk individuals, prior to potential illness onset, expand
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52 the evidence suggesting that cognitive subgroups might assist in identifying more
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1 biologically meaningful liability subtypes. In addition, studies in individuals at
2 clinical ultra-high risk (UHR) for psychosis reported either larger ⁴², smaller ⁴³ or no
3 differences ⁴⁴ in surface area compared to HC. Our findings suggest that stratification
4 based on cognition could contribute to clarify such variable findings, especially
5 considering that smaller surface area was associated with poorer premorbid
6 functioning in the UHR ⁴³.

7
8 In line with our second hypothesis the clusters differed in terms of PRS-COG but we
9 identified no significant between-cluster difference in terms of PRS-SZ and PRS-BP.
10 PRS-COG was significantly worse in the impaired cluster compared to the other two
11 clusters and to HCO. Our results overlap with those of a recent study that employed
12 high-dimensional clinical and cognitive data to cluster participants with SZ and BP
13 diagnoses into different psychosis subgroups ⁴⁵. The authors identified between-
14 cluster differences for PRS-EA but not for PRS-SZ or PRS-BP and emphasized the
15 potential role of symptom-based stratification to clarify genetic profiles and
16 functional outcomes using modular taxonomies ⁴⁵. Our results are also consistent with
17 those of a study that used both current and retrospective premorbid cognitive
18 assessments in an attempt to infer whether different developmental trajectories are
19 associated with different PRS profiles. Patients with SZ were grouped based on
20 whether their cognition was *preserved*, *deteriorated* or *compromised* ⁴⁶. All groups
21 had elevated PRS-SZ compared to HC. On the other hand, the preserved group had
22 PRS-COG and PRS-EA that were similar to HC, while the deteriorated and
23 compromised group had progressively more disadvantageous cognitive PRSs ⁴⁶. PRS-
24 SZ is estimated to explain about 8% of SZ risk, with one third of this polygenic risk
25 mediated through cognitive pathways ⁴⁷. Yet about 26% of the genetic variance for
26 SZ liability is associated with cognition-relevant pathways not captured by PRS-SZ
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⁴⁷. Cognitive heterogeneity in SZ is considered to be at least in part dependent on genetic factors that index cognition in the general population ²¹. Our results reinforce such perspective offering new insight from individuals prior to potential illness onset and across both SZ and BP high-risk populations.

Despite the important relationship between cognition and psychosocial functioning, there is only limited work examining familial concordance of functional outcomes. Studies that examined the potentially familial nature of several clinical domains in patients with SZ and their first-degree relatives identified functioning as the dimension with the highest concordance ⁴⁸. On the other hand, SZ, BP and cognition share substantial genetic variance yet it is not clear whether this reflects causality, pleiotropy, or a shared third factor such as brain structure ⁴⁹. We therefore examined the relationship between PRS-COG and psychosocial functioning and tested whether this was in part mediated by an effect of genes for cognition on the brain. We for the first time identified a significant positive relationship between PRS-COG and psychosocial functioning, yet no mediation through brain surface area. This is in keeping with the suggestion that cognitive deficits lie upstream of SZ liability, while changes in brain volume lie downstream, supporting a putative causal role of cognitive dysfunction in SZ liability ⁴⁹. The relationship between PRS-COG and psychosocial functioning that we identified further highlights the important relationship between genetic, cognitive and functioning variables along the SZ-BP continuum and their interdependent role in liability.

Our study has a number of strengths, in particular the current rather than retrospective assessment of cognition without the possible confounders of illness and medication. In addition the examination of both youth at risk of SZ and BP offers a transdiagnostic perspective to the design. At the same time, the fact that most of the

1 participants have yet to reach the mean age of onset for the examined disorders means
2 that our study is significantly limited in its possible conclusions by the lack of
3 outcome information. We hence cannot assess whether cluster membership or a
4 specific set of characteristics are predictors of future illness. The socioeconomic
5 status imbalance between the groups represents a further important limitation to our
6 work, as it is known to have a significant impact on brain development ⁵⁰. However,
7 socioeconomic status is also known to have an impact on cognitive development and
8 it accounts for about 20% of the variance in childhood IQ ⁵⁰. Having used a data
9 driven approach, it was not possible to balance groups based on demographic
10 variables, especially those that are known to have an effect on cognition itself. The
11 sex imbalance between clusters is another important demographic confounder to our
12 results, due to the differences in brain maturation, especially during puberty.
13 However, due to the limited size of the sample, we were not able to perform sex based
14 separate analyses. The size and sociodemographic characteristics of the sample hence
15 limited the generalizability of the results.

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39 Our findings expand the evidence suggesting that cognitive subtypes might aid the
40 identification of more biologically meaningful liability groups. They support views
41 suggesting that stratification based on cognition may help to elucidate diathesis
42 mechanisms across SZ and BP risk. Further work should dissect cognitive
43 heterogeneity to further clarify the relative role of neurodevelopmental mechanisms in
44 disease trajectories.

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Table 1: Demographic and Clinical Characteristics

	Intact (1) Mean (SD)	Intermediate (2) Mean (SD)	Impaired (3) Mean (SD)	HCO (4) Mean (SD)	Significance		
					F or χ^2	p	Bonferroni post hoc
Age	12.86 (3.05)	11.67 (2.87)	12.48 (2.89)	12.01 (2.87)	1.1	0.35	
Sex, M/F	23/11	19/21	14/3	30/39	11.79	0.008	
IQ	109.88 (10.82)	102.1 (12.82)	92.24 (14.84)	108.5 (12.48)	10.06	<0.001	1 vs 2 p=0.051 1 vs 3 p<0.001 2 vs 3 p=0.043 3 vs 4 p<0.001 4 vs 2 p=0.067
SES	52.34 (13.52)	46 (15.59)	38.44 (18.23)	51.52 (13.03)	4.495	0.005	1 vs 3 p=0.014 3 vs 4 p=0.09
CGAS	83.88 (11.17)	83.25 (10.66)	71.65 (14.32)	86.81 (6.95)	8.635	<0.001	1 vs 3 p=0.002 2 vs 3 p=0.003 3 vs 4 p<0.001
SOPS positive	0.97 (1.52)	1 (2.08)	0.75 (1.57)		0.113	0.89	
SOPS negative	1.16 (3.27)	0.86 (1.66)	2.56 (2.85)		2.45	0.092	
SOPS disorganized	1.13 (1.87)	0.83 (1.56)	2.38 (1.58)		4.72	0.012	1 vs 3 p=0.05 2 vs 3 p=0.01
SOPS total	4.26 (7.86)	3.11 (4.55)	7.13 (5.02)		2.14	0.096	
CGI	1.67 (1.02)	1.67 (0.98)	2.76 (1.3)		7.35	0.001	1 vs 3 p=0.003 2 vs 3 p=0.002

Note: CGAS= Children's Global Assessment Scale for psychosocial functioning; CGI=Clinical Global Impression, HCO=offspring of healthy control parents; SES=socioeconomic status; SOPS=Scale of Prodromal Symptoms

Table 2: Imaging Findings

GLOBAL BRAIN MEASURES								
	Intact (1) Mean (SE)	Intermediate (2) Mean (SE)	Impaired (3) Mean (SE)	HCO (4) Mean (SE)	F	p	q	Post hoc
Total intracranial Volume	1562680.6 (21169.07)	1537330.7 (19365)	1506245.5 (28754.54)	1534233.6 (17249.67)	1.032	0.381	0.381	
Total surface area	181909.16 (1323.25)	176378.75 (1192.59)	177312 (1856.62)	179657.03 (944.89)	3.777	0.012	0.036	1 vs 2 p=0.002 1 vs 3 p=0.04 4 vs 2 p=0.033
Mean cortical thickness	2.677 (0.014)	2.706 (0.012)	2.721 (0.019)	2.686 (0.01)	1.766	0.157	0.235	
REGIONAL SURFACE AREA								
Bilateral Cortical Brain Region	Intact (1) Mean (SE)	Intermediate (2) Mean (SE)	Impaired (3) Mean (SE)	HCO (4) Mean (SE)	F	p	q	Post hoc
Occipital Area	11346.95 (176.79)	11685.94 (164.72)	11822.43 (235.21)	11811.72 (159.24)	1.853	0.139	0.173	
Temporal Area	17667.35 (152.43)	17086.57 (140.4)	17021.51 (206.08)	17115.63 (127.49)	4.15	0.007	0.035	1 vs 2 p=0.013 1 vs 3 p=0.037 1 vs 4 p=0.048
Parietal Area	23806.55 (269.8)	22939.46 (247.11)	23185.18 (367.228)	23520.77 (222.58)	2.488	0.063	0.105	
Cingulate Area	3759.68 (51.79)	3714.38 (47.04)	3859.14 (71.18)	3724.39 (40.68)	1.125	0.341	0.341	
Frontal Area	31719.05 (247.37)	30623.95 (251.72)	30764.14 (372.72)	31279 (228.44)	3.758	0.013	0.032	1 vs 2 p=0.01 1 vs 3 p=0.056

Note: Summary table of global brain measures (above panel) and bilateral regional brain surface area (bottom panel). HCO=offspring of healthy control parents; SE=standard error; q=FDR adjusted p value.

Table 3: Polygenic Risk Scores for Schizophrenia, for Bipolar Disorder and for Cognition

	Intact (1) Mean (SE)	Intermediate (2) Mean (SE)	Impaired (3) Mean (SE)	HCO (4) Mean (SE)	Significance		
					F	p	Bonferroni post hoc
PRS-SZ	0.088 (0.177)	-0.079 (0.161)	0.204 (0.241)	0.073 (0.14)	0.394	0.757	
PRS-BP	-0.176 (0.181)	-0.129 (0.166)	0.342 (0.244)	0.018 (0.151)	1.313	0.273	
PRS-COG	0.098 (0.168)	0.095 (0.155)	-0.673 (0.238)	0.137 (0.156)	3.295	0.022	1 vs 3 p=0.054 2 vs 3 p=0.045 4 vs 3 p=0.016

Note: HCO=offspring of healthy control parents, PRS-BP=polygenic risk score for bipolar disorder, PRS-COG=polygenic risk score for cognitive function, PRS-SZ=polygenic risk score for schizophrenia, SE=standard error)

Figure 1: Polygenic Risk Score for Cognitive Performance

Figure 2: Mediation Analysis

Note: Independent variable (IV) = polygenic risk score for cognition, dependent variable (DV) = psychosocial functioning, proposed mediator (M) = total brain surface area

Figure 1

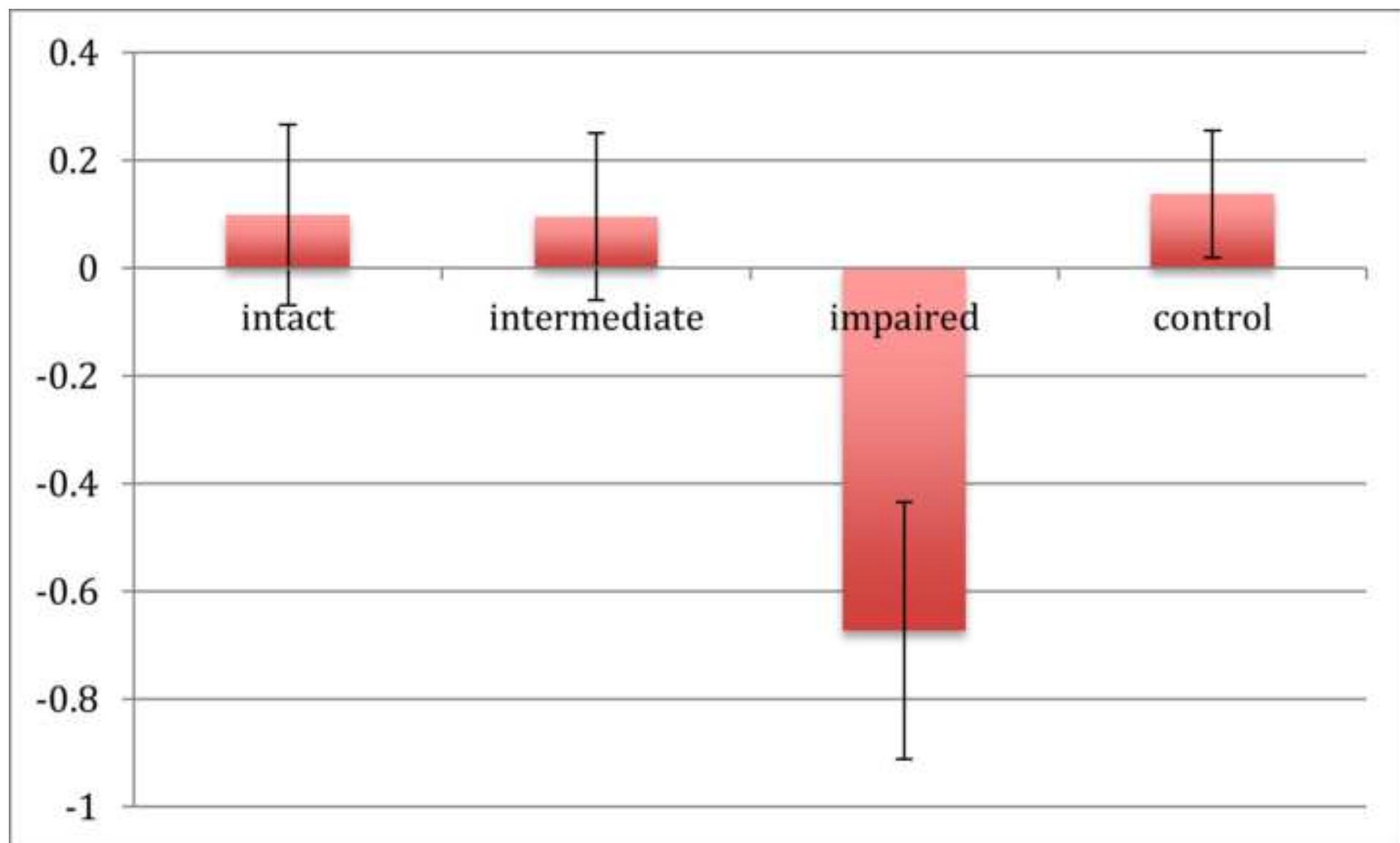
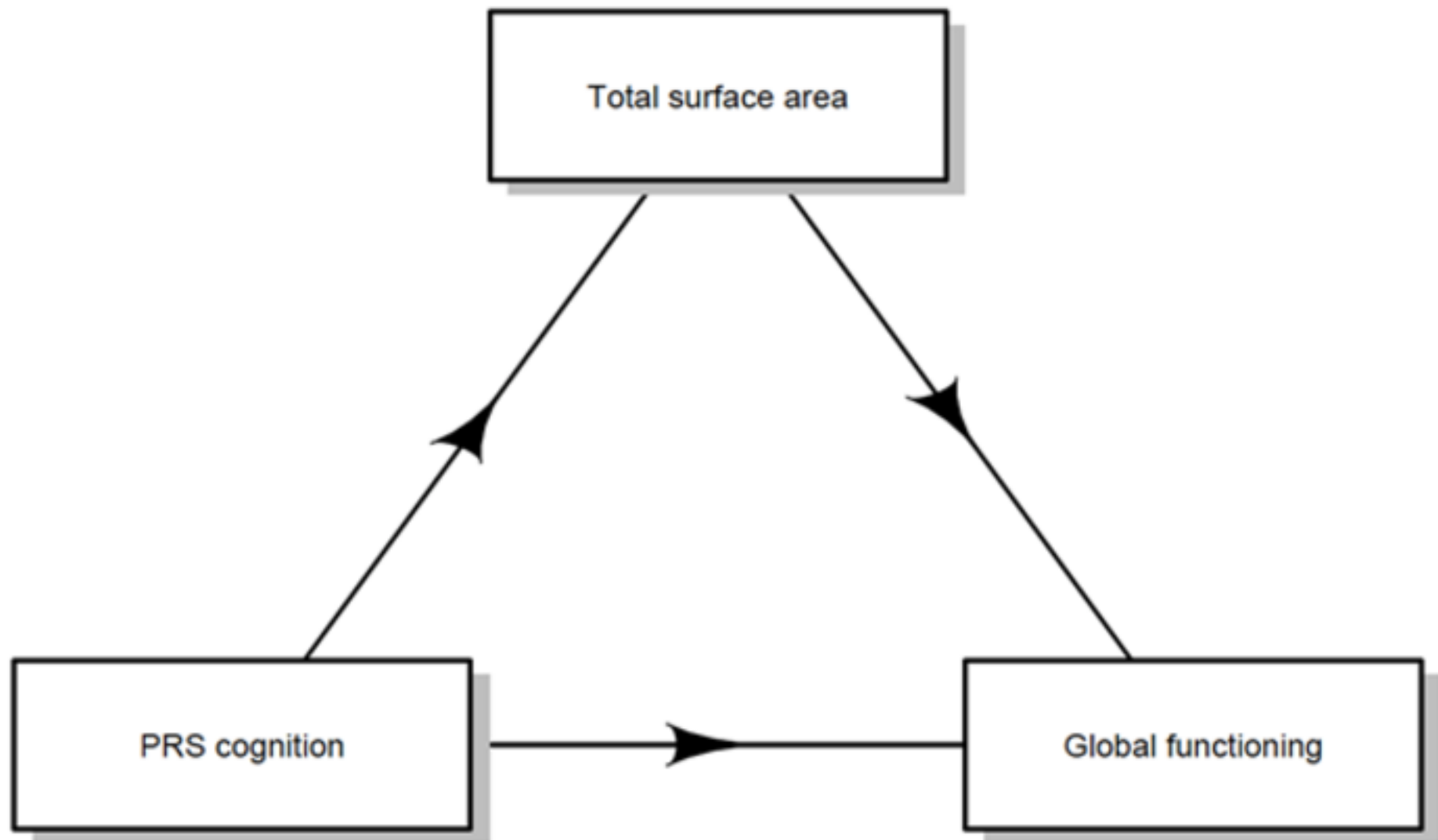


Figure 2



Lay summary

Schizophrenia and bipolar disorder can be accompanied by cognitive difficulties, sometimes observed long before the onset of the illness. We studied children who are at family risk for both disorders because they have an affected parent. We divided them in three groups: those with no cognitive difficulties, those with mild difficulties and those with more severe ones. We then studied the genetic characteristics of each of these groups as well as their brain structure.

Social media

New study @JAACAP examines the brain and genetic bases of cognitive difficulties in children at family risk for schizophrenia and bipolar disorder

Clinical guidance

We examined cognition in the offspring of parents with schizophrenia and bipolar disorder to assess the relative frequency of impairments in the two groups and to examine their genetic and structural brain correlates.

Impairments were observed in both groups yet not evenly, with a higher frequency in the children of parents with schizophrenia, but also in bipolar offspring, though in a smaller proportion

Impairments were associated with reduced brain surface area and worse polygenic risk scores for cognition, but not with polygenic risk scores for either schizophrenia or for bipolar disorder

We observed a relationship between genes for cognition and psychosocial functioning but inferences in terms of prediction of illness will only be possible once participants reach the age of onset for the examined disorders

Supplement 1: Biological samples collection and storage

Blood samples were collected using BD Vacutainer® tubes, with K2 EDTA (Becton Dickinson, Franklin Lakes, New Jersey). Genomic DNA was extracted with the MagNA Pure LC DNA isolation Kit using an LC MagNA Pure system (Roche Diagnostics GmbH, Mannheim, Germany). Saliva samples were collected using the Oragene DNA Sample collection Kit (OG-500, DNA Self-Collection Kit, Genotek, Ottawa, Ontario, Canada) and DNA was extracted according to the manufacturer's protocol. Both samples were stored at -80°C. DNA concentration and quality were measured spectrophotometrically using a NanoDrop® 2000 (Thermo Fisher Scientific, Epsom, Surrey, UK).

Supplement 2: Imaging acquisition and processing

Scanning parameters for each of the two scanners employed are reported in Table S1.

	TE (ms)	TR (ms)	Dimensions (mm)	Slices	FOV	Matrix	FA
Siemens Magnetom Trio (Barcelona)	3.01	2300	1.0x0.94x0.94	240	240x240	256x256	09°
Philips Intera (Madrid)	9.2	25	1.0x0.94x0.94	175	240x240	256x256	30°

Table S1 Image acquisition parameters

All images were processed using Freesurfer v7.2.0, following an automated pipeline that is described and freely available for download online (<https://surfer.nmr.mgh.harvard.edu/>). Measures of mean cortical thickness and total surface area were averaged between hemispheres since no laterality effects were expected. Lobar measures were computed and divided using the mri_annotation2label command included in the FreeSurfer package.

Supplementary Results

Supplement 3: Participants

The original sample in which the cluster analysis was performed included 220 participants. Of these 177 had provided a biological sample for genotyping. 8 participants were excluded based on sex check and 5 participants due to heterozygosity (not within +-3SD from the mean).

A further 2 subjects did not have MRI information and 2 were excluded due to the quality of segmentation.

	Intact	Intermediate	Impaired	HCO
Current study	34	40	17	69
Previous Study	48	64	27	81
Proportion included	0.71	0.63	0.63	0.85

Table S2 Proportion of participants included relative to the original sample

Participants that were not included (n=60) did not significantly differ from those included (n=160) in terms of the following variables:

	Included Mean (SD)	Not Included Mean (SD)	t or χ^2	p
Age	12.19 (2.92)	12.13 (3.09)	0.142	0.887
Sex. M/F	86/74	34/26	0.15	0.699
IQ	105.45 (13.53)	102.73 (14.51)	1.266	0.207
SES	47.71 (14.94)	44.67 (13.7)	1.379	0.169
GCAS	83.15 (11.33)	80.35 (13.87)	1.533	0.127

Table S3 Characteristics of included and non-included participants

Supplement 4: Cognition by group

	Intact Mean (S.D.)	Intermediate (2) Mean (S.D.)	Impaired (3) Mean (S.D.)	Controls (4) Mean (S.D.)	Significance		Significant post-hoc comparisons
					F	p value	
Attention	0.17 (0.49)	-0.12 (0.48)	-0.34 (0.84)	0 (0.67)	2.921	0.036	1 vs 3 p=0.037
Working memory	0.25 (0.74)	-0.49 (0.86)	-1.14 (0.91)	-0.03 (0.87)	12.398	<0.001	1 vs 2 p=0.001 1 vs 3 p<0.001 2 vs 4 p=0.039 3 vs 4 p<0.001
Processing speed	-0.1 (0.81)	-0.39 (0.77)	-1.39 (0.91)	0 (0.83)	13.829	<0.001	1 vs 3 p<0.001 2 vs 3 p<0.001 3 vs 4 p<0.001
Verbal memory	0.01 (0.57)	-0.33 (0.51)	-1.46 (0.49)	-0.05 (0.65)	28.627	<0.001	1 vs 3 p<0.001 2 vs 3 p<0.001 3 vs 4 p<0.001
Visual memory	-0.03 (0.56)	-0.63 (0.69)	-1.66 (0.49)	-0.04 (0.7)	29.349	<0.001	1 vs 2 p=0.002 1 vs 3 p<0.001 2 vs 3 p<0.001 2 vs 4 p<0.001 3 vs 4 p<0.001
Executive function	1.02 (0.4)	-0.43 (0.73)	0.12 (0.83)	-0.02 (0.75)	26.357	<0.001	1 vs 2 p<0.001 1 vs 3 p<0.001 1 vs 4 p<0.001 2 vs 4 p=0.032

Table S4 Cognition by group

Groups were compared in terms of z-transformed measures of attention, working memory, processing speed, verbal memory, visual memory and executive function. There was a main affect of group for all the examined domains (Table S6).

In terms of attention the impaired cluster performed significantly poorer compared to the intact. In terms of processing speed and verbal memory the impaired cluster performed significantly poorer than the other two clusters and HC participants. For working memory and visual memory the intact cluster and HC participants outperformed the intermediate and the impaired clusters, but for visual memory, the intermediate cluster also outperformed the impaired. Finally, for executive function, the intact cluster outperformed the other two clusters and HC participants, while the latter also outperformed the intermediate cluster.

Supplement 5: Pharmacological treatment

The clusters did not significantly differ in terms of pharmacological treatment, which in all cases was administered for the treatment of ADHD. None of the HC participants was receiving pharmacological treatment (Table S5).

	Intact	Intermediate	Impaired	χ^2	p
Pharmacological treatment				2.890	0.236
Yes	4 (11.8%)	3 (7.5%)	4 (23.5%)		
No	30 (88.2%)	37 (92.5%)	13 (76.5%)		

Table S5 Pharmacological treatment

	Intact	Intermediate	Impaired	HC	χ^2	p
Alcohol					1.662	0.645
Yes	3 (8.8%)	1 (2.5%)	1 (5.9%)	3 (4.3%)		
No	31 (91.2%)	39 (97.5%)	16 (94.1%)	66 (95.7%)		
Tobacco					1.972	0.578
Yes	2 (5.9%)	1 (2.5%)	1 (5.9%)	1 (1.4%)		
No	32 (94.1%)	39 (97.5%)	16 (94.1%)	68 (98.6%)		
Cannabis					3.097	0.377
Yes	1 (2.9%)	1 (2.5%)	1 (5.9%)	0 (0%)		
No	33 (97.1%)	39 (97.5%)	16 (94.1%)	69 (100%)		

Table S6 Alcohol and substance use

Supplement 6: Recruitment center

Participants recruited at the two sites didn't differ in terms of age ($t=0.928$, $p=0.355$), sex ($\chi^2=0.251$, $p=0.616$) or the proportion assigned to each of the clusters ($\chi^2=2.133$, $p=0.545$) (Table S7)

	Intact	Intermediate	Impaired	HCO
Hospital Clinic	26	32	13	47
Hospital Gregorio	8	8	4	22

Table S7 Recruitment center

Imaging Results

Bilateral Cortical Brain Region	Intact (1) Mean (SE)	Intermediate (2) Mean (SE)	Impaired (3) Mean (SE)	HC (4) Mean (SE)	F	p	q	Post hoc
Occipital Thickness	2.133 (0.016)	2.165 (0.014)	2.197 (0.023)	2.141 (0.011)	2.438	0.068	0.34	
Parietal Thickness	2.576 (0.018)	2.620 (0.016)	2.621 (0.025)	2.593 (0.013)	1.551	0.205	0.34	
Temporal Thickness	2.941 (0.018)	2.963 (0.016)	2.981 (0.025)	2.956 (0.013)	0.701	0.553	0.55	
Cingulate Thickness	2.147 (0.017)	2.166 (0.015)	2.194 (0.024)	2.158 (0.012)	0.912	0.437	0.55	
Frontal Thickness	2.790 (0.015)	2.825 (0.013)	2.839 (0.021)	2.802 (0.01)	1.962	0.123	0.31	

Table S8: Summary table of bilateral regional cortical thickness for each of the clusters and HCO (SE=standard error; q=FDR adjusted p)

Bilateral Subcortical Brain Region	Intact (1) Mean (SE)	Intermediate (2) Mean (SE)	Impaired (3) Mean (SE)	HC (4) Mean (SE)	F	p	q	Post hoc
Lateral Ventricle	4745.68 (370.01)	4155.69 (335.93)	5364.42 (526.54)	4429.93 (255.71)	1.378	0.252	0.67	
Thalamus	7964.01 (103.39)	8094.53 (93.35)	7905.85 (147.64)	7912.28 (78.38)	0.861	0.463	0.62	
Caudate	3920.30 (55.12)	3946.61 (52.09)	3998.30 (71.5)	3864.19 (53)	0.844	0.471	0.54	
Putamen	5924.87 (90.83)	6101.08 (82.19)	5831.86 (125.77)	5961.41 (69.19)	1.371	0.255	0.51	
Pallidum	1761.62 (39.1)	1777.52 (35.25)	1741.23 (54.66)	1762.26 (28.48)	0.111	0.954	0.95	
Hippocampus	4138.41 (49.34)	4263.14 (45.15)	4174.88 (67.23)	4172.73 (40.5)	1.5	0.216	0.95	
Amygdala	1694.04 (23.59)	1732.36 (21.51)	1686.69 (32.29)	1690.82 (18.96)	0.958	0.414	0.66	
Accumbens	588.01 (12.52)	611.05 (11.41)	589.93 (17.14)	580.75 (10.03)	1.452	0.23	0.92	

Table S9: Summary table of bilateral subcortical regional volumes for each of the clusters and HCO (SE=standard error; q=FDR adjusted p)

Supplement 7: Mediation analysis

	Estimate	Std Error	t	p
Total Effect (IV on DV)	2.1159	0.8083	2.618	0.009
IV effect on mediator	-79.32	1415.1	-0.056	0.955

Table S10: Mediation analysis results

- Total effect: Effect of PRS-COG on CGAS
- IV effect on mediator: Effect of PRS-COG on total surface area

The relationship between PRS-COG and CGAS was very similar to that observed in the whole sample when examining high-risk participants and HC independently, yet it did not reach significance in either group.