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## The Association Between Familial Risk and Brain Abnormalities Is Disease Specific: An ENIGMA-Relatives Study of Schizophrenia and Bipolar Disorder

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### ABSTRACT

**BACKGROUND:** Schizophrenia and bipolar disorder share genetic liability, and some structural brain abnormalities are common to both conditions. First-degree relatives of patients with schizophrenia (FDRs-SZ) show similar brain abnormalities to patients, albeit with smaller effect sizes. Imaging findings in first-degree relatives of patients with bipolar disorder (FDRs-BD) have been inconsistent in the past, but recent studies report regionally greater volumes compared with control subjects.

**METHODS:** We performed a meta-analysis of global and subcortical brain measures of 6008 individuals (1228 FDRs-SZ, 852 FDRs-BD, 2246 control subjects, 1016 patients with schizophrenia, 666 patients with bipolar disorder) from 34 schizophrenia and/or bipolar disorder family cohorts with standardized methods. Analyses were repeated with a correction for intracranial volume (ICV) and for the presence of any psychopathology in the relatives and control subjects.

**RESULTS:** FDRs-BD had significantly larger ICV ( $d = +0.16$ ,  $q < .05$  corrected), whereas FDRs-SZ showed smaller thalamic volumes than control subjects ( $d = -0.12$ ,  $q < .05$  corrected). ICV explained the enlargements in the brain measures in FDRs-BD. In FDRs-SZ, after correction for ICV, total brain, cortical gray matter, cerebral white matter, cerebellar gray and white matter, and thalamus volumes were significantly smaller; the cortex was thinner ( $d < -0.09$ ,  $q < .05$  corrected); and third ventricle was larger ( $d = +0.15$ ,  $q < .05$  corrected). The findings were not explained by psychopathology in the relatives or control subjects.

**CONCLUSIONS:** Despite shared genetic liability, FDRs-SZ and FDRs-BD show a differential pattern of structural brain abnormalities, specifically a divergent effect in ICV. This may imply that the neurodevelopmental trajectories leading to brain anomalies in schizophrenia or bipolar disorder are distinct.

**Keywords:** Bipolar disorder, Familial risk, Imaging, Meta-analysis, Neurodevelopment, Schizophrenia

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Schizophrenia and bipolar disorder are highly heritable disorders with partially overlapping symptoms and a genetic correlation ( $r_g$ ) of 0.60–0.68 (1–3). Both disorders are characterized by structural brain abnormalities, with smaller total brain and hippocampal volumes, on average, and larger ventricular volumes. These are among the most consistent and robust structural findings, albeit with smaller effect sizes in patients with bipolar disorder (4–12). On one hand, the shared genetic liability between schizophrenia and bipolar disorder (1–3) is partly reflected in the brain by overlapping findings of smaller white matter volumes and common areas of thinner cortex, suggesting that the disorders share genetic (possibly neurodevelopmental) roots (13). On the other hand, disease-specific brain abnormalities were also reported in the same twin study; genetic liability for schizophrenia was associated with thicker right parietal cortex, whereas genetic liability for bipolar disorder was associated with larger intracranial volume (ICV) (13).

Family members of patients can represent individuals at familial risk for the disorder who do not themselves have confounds, such as medication or illness duration, and can therefore provide unique insight into the effect of familial risk for the disorder on the brain. Multiple imaging studies have investigated individuals at high familial risk for schizophrenia and/or bipolar disorder, but results of these often small studies have been variable. First-degree relatives of patients with schizophrenia (FDRs-SZ) tend to show smaller brain volumes and larger ventricle volumes compared with control subjects (14,15). In contrast, first-degree relatives of patients with bipolar disorder (FDRs-BD) show regionally larger volumes (16–26). Many of these schizophrenia and bipolar disorder family studies grouped all FDRs together regardless of kinship. It remains unclear whether structural brain abnormalities in high-risk individuals are consistent across FDRs, or whether they vary depending on the generational relationship with the proband. In addition, a few studies compared brain structure between FDRs-BD and FDRs-SZ directly, usually in cohorts of modest sample sizes (9,13,27–30). These studies showed brain abnormalities both specific and overlapping for FDRs-SZ and FDRs-BD; if anything, findings were more pronounced in FDRs-SZ than FDRs-BD.

Large-scale multicenter studies offer increased power and generalizability to evaluate the pattern and extent of brain variation in FDRs-BD and FDRs-SZ. Through the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA)-Relatives Working Group, we have performed meta-analyses of magnetic resonance imaging data sets consisting of FDRs-SZ and/or FDRs-BD, probands, and matched control participants on harmonized global and subcortical brain measures. For each disorder, relatives were analyzed as a group as well as per relative type, i.e., monozygotic co-twins, dizygotic co-twins, offspring, siblings, and parents. To investigate potential confounders, analyses were performed both with and without correction for ICV and with and without a correction for having a psychiatric diagnosis in the relatives and control subjects. The latter correction was performed by 1) adding a single dummy variable coding for the presence of any psychiatric diagnosis and 2) by comparing only the healthy relatives with the healthy control subjects. We hypothesized that

FDRs-SZ (as a group) would exhibit a pattern of brain volume abnormalities similar to patterns observed in patients, but with smaller effect sizes. Based on dissimilarities in the literature between FDRs-SZ and FDRs-BD, we expected divergent effect sizes. Furthermore, we explored the pattern and extent of brain volume abnormalities per relative type.

## METHODS AND MATERIALS

### Study Samples

This study included 6008 participants from 34 family cohorts. In total, 1228 FDRs-SZ (49 monozygotic co-twins, 62 dizygotic co-twins, 171 offspring, 842 siblings, 104 parents), 852 FDRs-BD (41 monozygotic co-twins, 48 dizygotic co-twins, 443 offspring, 302 siblings, 18 parents), 2246 control subjects, 1016 patients with schizophrenia, and 666 patients with bipolar disorder were included (Tables 1 and 2). All cohorts included their own control participants. Control subjects did not have a family history of schizophrenia or bipolar disorder. FDRs-SZ or FDRs-BD are defined by having a first-degree family member with schizophrenia or bipolar disorder, respectively, and not having experienced (hypo)mania and/or psychosis themselves. Several cohorts allowed FDRs-SZ, FDRs-BD, or control subjects to have psychiatric diagnoses other than schizophrenia or bipolar disorder (Tables 1 and 2). Demographic characteristics for each cohort and their inclusion criteria are summarized in Tables 1 and 2 and Supplemental Table S1. All study centers obtained approval from their respective medical ethics committee for research following the Declaration of Helsinki. Informed consent was obtained from all participants (and/or parent guardians in the case of minors).

### Image Acquisition and Processing

Structural T1-weighted brain magnetic resonance imaging scans were acquired at each research center (see Supplemental Table S2 for acquisition parameters of each cohort). Cortical and subcortical reconstruction and volumetric segmentations were performed with the FreeSurfer pipeline (see Table S2 for FreeSurfer version and operating system used in each cohort) (<http://surfer.nmr.mgh.harvard.edu/fswiki/recon-all/>) (31). The resulting segmentations were quality checked according to the ENIGMA quality control protocol for subcortical volumes (<http://enigma.ini.usc.edu/protocols/imaging-protocols/>). Global brain measures (i.e., ICV [estimated Total Intracranial Volume from FreeSurfer], total brain [including cerebellum, excluding brainstem], cortical gray matter, cerebral white matter, cerebellar gray and white matter, third and lateral ventricle volume, surface area, and mean cortical thickness) and subcortical volumes (i.e., thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and accumbens) were extracted from individual images (32,33).

### Statistical Meta-analyses

All statistical analyses were performed using R (<http://www.r-project.org>). Linear mixed model analyses were performed within each cohort for bipolar disorder and schizophrenia separately, comparing relatives (per relative type) with control subjects and, if present, patients with control subjects, while taking family relatedness into account (<http://CRAN.R-project>.





org/package=nlme) (34). Given known age and sex effects on brain measures, we included centered age, age squared, and sex as covariates. Brain measures were corrected for lithium use at time of scan (yes/no) in patients with bipolar disorder only. Analysis of multiscanner studies included binary dummy covariates for  $n-1$  scanners. Cohen's  $d$  effect sizes and 95% confidence intervals were calculated within each cohort separately and pooled per disorder for each relative type, for all relatives, and for patients as a group, using an inverse variance-weighted random-effects meta-analysis. All random-effects models were fitted using the restricted maximum likelihood method. False discovery rate ( $q < .05$ ) thresholding across all phenotypes was used to control for multiple comparisons for each pairwise analysis between relatives, patients, and control subjects or between the different relative types (35). Analyses were performed locally by the research center that contributed the cohort, using codes created within the ENIGMA-Relatives Working Group (scripts available on request). The focus of this study is on first-degree relatives, but patient effects were also computed to show that the effects in patients are in line with earlier work (4–12). Effect sizes were statistically compared between FDRs-BD and FDRs-SZ, FDRs-BD and patients with bipolar disorder, and FDRs-SZ and patients with schizophrenia, and between the different relative types within one disorder (Supplemental Methods). The latter analysis was performed only when more than one cohort was included per relative type.

The regional specificity of the findings was examined by repeating the analyses of the global brain measures and subcortical volumes with ICV added as a covariate. In addition, we repeated the analyses to investigate the effect of psychopathology in the relatives and control subjects using two different approaches. First, we added a single dummy variable for relatives and control subjects with a DSM “No diagnosis” or ICD-9 code V71.09 (other diagnosis = 1, V71.09 = 0). Second, we compared healthy relatives with healthy control subjects. Finally, effects of age were examined using meta-regressions.

## RESULTS

### Patients

Effects in patients with schizophrenia and bipolar disorder were not the main focus of this study. In short, a thinner cortex and smaller thalamus volume were found in patients with bipolar disorder ( $d < -0.33$ ,  $q < .05$  corrected); in patients with schizophrenia, smaller volumes of total brain, cortical gray matter, cerebral white matter, cerebellar gray and white matter, thalamus, hippocampus, amygdala, and accumbens, thinner cortex ( $d < -0.18$ ,  $q < .05$  corrected), and larger volumes of the lateral ventricles, third ventricle, caudate, pallidum, and putamen ( $d > +0.16$ ,  $q < .05$  corrected) were found. The findings are summarized in Figures 1 and 2, Supplemental Figure S1i–xvii, and Supplemental Tables S3 and S4.

### FDRs-BD and FDRs-SZ vs. Control Subjects

FDRs-BD had significantly larger ICVs than control subjects ( $d = +0.16$ ,  $q < .05$  corrected) (Figures 1A and 2A, Supplemental Figure S1i–xvii, and Supplemental Table S3). FDRs-SZ had significantly smaller thalamic volume than control subjects

( $d = -0.12$ ,  $q < .05$  corrected) (Figures 1A and 2A, Supplemental Figure S1i–xvii, and Supplemental Table S3). When comparing the effect sizes of FDRs-BD and FDRs-SZ directly, FDRs-BD had significantly larger ICV, surface area, total brain, cortical gray matter, cerebral white matter, cerebellar gray matter, thalamus, and accumbens volumes and smaller third ventricle volumes than FDRs-SZ ( $q < .05$  corrected) (Supplemental Table S3). For all nominally significant effect sizes ( $p < .05$  uncorrected, 2-tailed) and comparisons, see Supplemental Table S3.

### Regional Specificity of Findings: Correction for ICV

When controlling for ICV, there were no significant differences in brain measures between FDRs-BD and control subjects (Figures 1B and 2B and Supplemental Table S4). In contrast, in FDRs-SZ, total brain, cortical gray matter, cerebral white matter, cerebellar gray and white matter, and thalamus volumes were significantly smaller, cortex was thinner ( $d < -0.09$ ,  $q < .05$  corrected), and third ventricle was larger ( $d = +0.15$ ,  $q < .05$  corrected) than in control subjects (Figures 1B and 2B and Supplemental Table S4). FDRs-BD had significantly larger total brain, cortical, and cerebellar gray matter volumes and smaller third ventricle volumes than FDRs-SZ ( $q < .05$  corrected) (Supplemental Table S4).

### First-Degree Relatives Subtype Analyses

None of the effect sizes comparing FDRs-BD and FDRs-SZ subtypes with control subjects survived correction for multiple comparisons. Direct comparison between the different relative subtypes showed some significant differences between groups; see Supplemental Tables S7 and S8, Supplemental Figure S1i–xvii and Supplemental Results.

### Psychopathology in Relatives

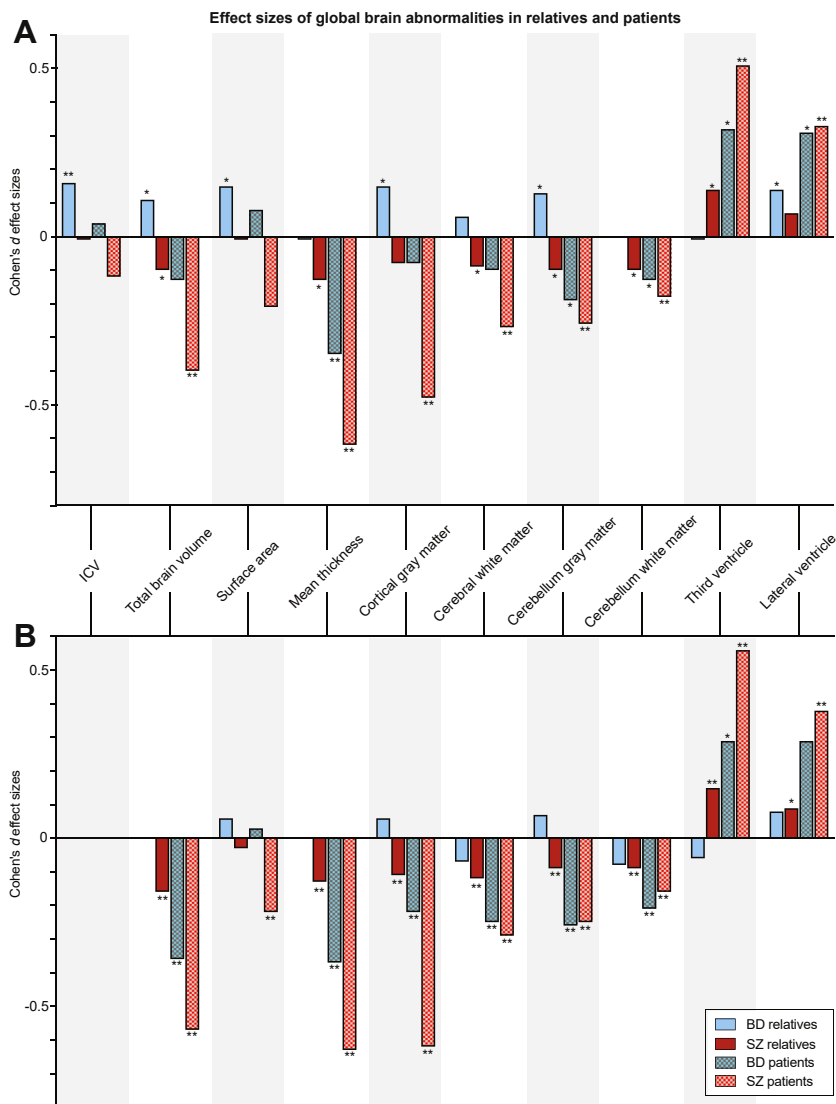
Psychiatric diagnoses other than bipolar disorder or a psychotic disorder were present in 40.4% of FDRs-BD, 31.5% of FDRs-SZ, 12.6% of control subjects in the bipolar sample, and 9.0% of control subjects in the schizophrenia sample (Tables 1 and 2). Controlling for any diagnosis by adding affected status (1 = yes/0 = no) as a covariate in the analysis did not change the pattern of findings in either FDRs-BD or FDRs-SZ (Supplemental Tables S9 and S10). Also, when comparing only healthy relatives with healthy control subjects, the pattern was similar (Supplemental Tables S11 and S12).

### Effect of Age

Meta-regression analyses showed no relationship between age and FDRs-BD effect sizes (Supplemental Table S13 and Figure S2i–xvii). A positive relationship between age and FDRs-SZ effect sizes reached nominal significance only in the amygdala ( $p = .008$ , which did not survive false discovery rate correction for multiple comparisons) (Supplemental Table S13 and Figure S2i–xvii).

## DISCUSSION

This ENIGMA-Relatives initiative allowed for the largest examination to date of FDRs-BD and FDRs-SZ. Through meta-analysis, we investigated whether harmonized subcortical and global brain measures differed between FDRs-BD and FDRs-SZ and control subjects and whether these brain



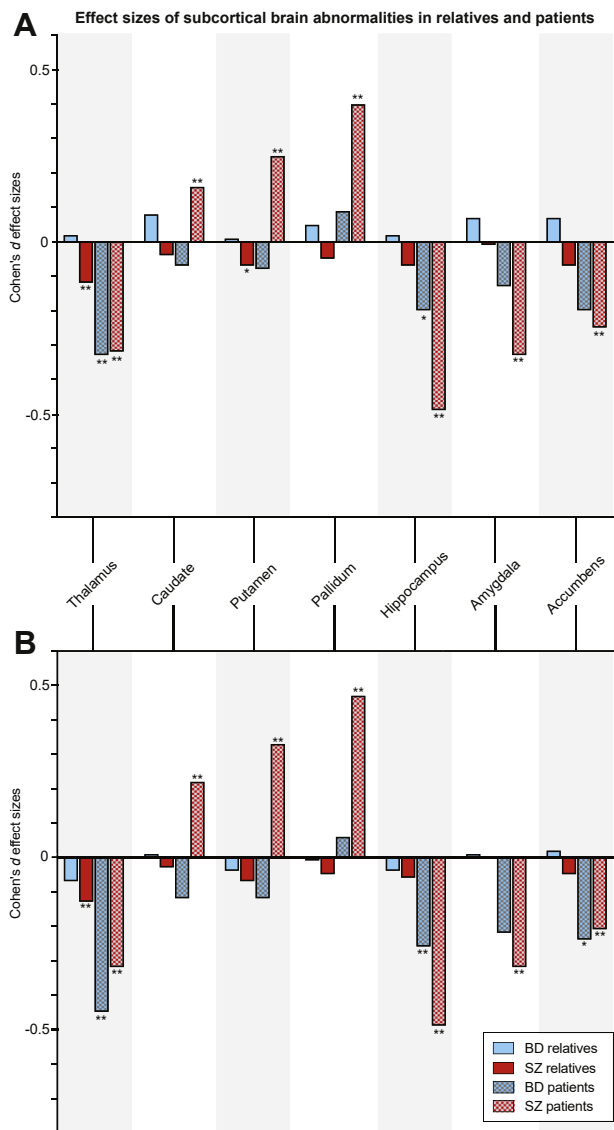
**Figure 1.** (A) Cohen's *d* effect sizes comparing relatives and patients with bipolar disorder (BD) (blue) and relatives and patients with schizophrenia (SZ) (red) with control subjects for global brain measures, (B) controlled for intracranial volume (ICV). \*Nominally significant effect sizes ( $p < .05$ , uncorrected); \*\* $q < .05$ , corrected.

measures differed between the different relative types. The main findings were that 1) FDRs-BD had larger ICVs, whereas FDRs-SZ showed smaller thalamic volumes compared with control subjects; 2) in FDRs-BD, ICV explained enlargements in other brain measures, whereas in FDRs-SZ, brain volumes and thickness became significantly smaller than in control subjects after correction for ICV; 3) abnormalities differed between the relative types, but no clear pattern was detected; and 4) the findings were not confounded by other psychiatric diagnoses in the relatives and control subjects.

Effects in patients with schizophrenia and bipolar disorder were in line with prior studies (4–12). In contrast to smaller brain volumes in patients with bipolar disorder (7,8), we found larger brain volumes in their relatives. This is in keeping with other studies, which have reported larger regional gray matter volumes in participants at genetic risk (16–26). As expected, FDRs-SZ had smaller brain volumes, similar to findings in

patients with schizophrenia (6,10–12), but with smaller effect sizes, in line with a previous retrospective meta-analysis and a review (14,36). Effect sizes in both FDRs-SZ and FDRs-BD are small ( $|d| \leq 0.16$ ), suggesting that the brain abnormalities in individuals at familial risk are subtle and can be detected only with large sample sizes. These small effect sizes and potential subtle differences could still be meaningful, as they may give information on the familial background of brain deficits in disease. That said, it remains unclear whether brain deficits with these small effect sizes have functional or clinical relevance for FDRs-BD and FDRs-SZ.

Bipolar disorder and schizophrenia have a partially overlapping genetic etiology, with a genetic correlation of  $r_g = 0.60$ – $0.68$  based on population and genome-wide association studies (1–3), suggesting that they share to some extent the same risk genes. However, combined large genome-wide association studies of schizophrenia and bipolar disorder have



**Figure 2.** (A) Cohen's *d* effect sizes comparing relatives and patients with bipolar disorder (BD) (blue) and relatives and patients with schizophrenia (SZ) (red) with controls for subcortical volumes, (B) controlled for intracranial volume. \*Nominally significant effect sizes ( $p < .05$ , uncorrected); \*\* $q < .05$ , corrected.

also identified unique risk factors associated with each of these disorders (37). That FDRs-BD and FDRs-SZ show different global brain volume effects compared with control subjects implies that these brain abnormalities are associated with genetic variants unique to each disorder.

Twin studies have shown that schizophrenia (38–41) and bipolar disorder (42,43) have a shared genetic origin for brain volume, and overlapping brain abnormalities have been reported between the two patient groups (4,5,9,13). However, the available evidence for an association between common variants in both schizophrenia and bipolar disorder and brain volume is inconsistent (37,44–46). For example, Smeland *et al.* (45) used novel conditional false discovery rate methodology

and identified 6 shared loci between intracranial, hippocampus, and putamen volumes and schizophrenia, whereas no significant genetic correlation was reported in another study that applied standard statistical tools (44). Genetic risk for bipolar disorder was unrelated to the genetic variants associated with brain measures (37,46). This could suggest either that rare genetic variants, such as copy number variants that are shared between relatives and probands, lead to brain abnormalities or that nongenetic overlap, i.e., shared environmental factors, leads to brain abnormalities in the family members.

The enlargement in several brain measures in FDRs-BD was driven by a larger ICV, whereas the decrements in brain measures in FDRs-SZ were more pronounced when controlling for ICV. This suggests that in contrast to the global ICV finding in FDRs-BD, brain abnormalities in FDRs-SZ not only are a global effect but also represent more regional differences in individuals at familial risk for schizophrenia. ICV reaches its maximum size between the ages of 10 and 15 (47,48); therefore, ICV may be interpreted as a direct marker for neurodevelopment. Indeed, both schizophrenia and bipolar disorder have been characterized as neurodevelopmental disorders (49–51); abnormal neurodevelopment may play a larger role in the onset of schizophrenia than bipolar disorder (52–54). This is in line with differential trajectories of IQ development and school performance found in relation to risk for schizophrenia and bipolar disorder, showing respectively poorer cognitive performance or even decreases over time years before schizophrenia onset and a U-shaped relationship between IQ and later development of bipolar disorder (53). This is also in keeping with a previous study, which found advanced brain age relative to chronological age in participants in early stages of schizophrenia, but not in participants in early stages of bipolar disorder (55). Given the discrepancy in ICV findings between FDRs-BD and FDRs-SZ, individuals at familial risk for either bipolar disorder or schizophrenia may deviate during early neurodevelopment in a disease-specific manner.

Interestingly, in contrast to FDRs-BD, patients with bipolar disorder did not show an ICV enlargement, confirming previous findings in a large meta-analysis (7). In the early stages of the disease, however, regional increases have been reported (21,22,24,26,56,57). Given the positive relationship between genetic risk for bipolar disorder and ICV reported in twins (13), one could argue that the genetic liability for bipolar disorder leads to a larger ICV as represented in our findings of larger ICV in FDRs-BD. That combination of a genetic predisposition for increased ICV and an ICV that is similar between patients with bipolar disorder and control subjects may imply that patient ICV is decreased owing to illness-related factors. Therefore, the discrepancy in ICV findings between patients with bipolar disorder and their relatives might suggest that smaller ICV in patients compared with their relatives can be regarded as a (possibly prodromal) disease effect, similar to what has been reported in schizophrenia. Alternatively, larger ICV in FDRs-BD could represent a relative resilience to developing bipolar disorder, as was suggested in a prior report on hippocampal shape abnormalities in co-twins without bipolar disorder (58).

The pattern and extent of brain abnormalities varied with respect to the type of relationship to the proband. This again suggests a role for environmental influences, as all FDRs share



approximately 50% of their common genetic variants with the affected proband (except for monozygotic co-twins). Given that many environmental risk factors, e.g., age, childhood trauma, physical inactivity, and famine, are associated with brain structure (59–61), environmental risk and/or gene-by-environment interplay are likely also associated with differences in brain abnormalities in individuals at familial risk for schizophrenia or bipolar disorder. However, despite the large sample size, we did not find a consistent pattern of abnormalities among different relative types. Power may still not be sufficient to detect these subtle differences. Alternatively, there are many environmental factors that are unique for an individual—and thus not specific to the relative type—and these could have influenced brain structure.

Psychopathology is more prevalent in individuals at familial risk for either bipolar disorder or schizophrenia than in the general population; for example, offspring studies have shown that 55% to 72% of individuals with a parent with bipolar disorder or schizophrenia developed a lifetime mental disorder (62,63). We showed that the presence of a psychiatric diagnosis in relatives and control subjects did not influence our findings. This suggests that brain abnormalities seen in the relatives represent the familial liability for the disorder and not the presence of psychopathology.

Some limitations should be considered in interpreting the results. This study is a meta-analysis of multiple cohorts from research centers around the world, with heterogeneity across samples (among others, acquisition protocols, field strength, FreeSurfer version, inclusion and exclusion criteria). Meta-analysis will find consistent effects despite this variance but cannot remove all sources of heterogeneity. However, clinical heterogeneity within and across sites is representative of the broad, clinically varied, and ecologically valid nature of bipolar disorder and schizophrenia and allows generalizable alterations to be detected. One source of heterogeneity in the offspring in particular might also be the substantial age differences between the different offspring cohorts. Both adult and children/adolescent offspring cohorts were included in the analyses, and the fact that the brains of the child and adolescent offspring have not reached adult size might have influenced the findings of the overall offspring effects. In addition, inclusion criteria varied with respect to psychopathology in FDRs or control subjects at the different research centers. For example, some cohorts included only healthy relatives, yet others included relatives with other psychiatric diagnosis (except for having the disorder itself). We accounted for this with additional analyses covarying for any diagnosis or assessing only the healthy relatives. These approaches might not be sufficient. In addition, the composition of the FDRs-SZ and FDRs-BD groups differed. FDRs-SZ had a greater sample size and consisted in particular of more siblings, whereas there were more offspring in the FDRs-BD group. Finally, the discrepancy in ICV between FDRs-BD and FDRs-SZ may be associated with current IQ or parental socioeconomic status (SES). Both IQ and parental SES have been associated with brain structure (64–67). This might suggest that the larger ICV found in FDRs-BD is related to higher IQ or parental SES. Lower IQ has been reported in FDRs-SZ (68). However, the literature regarding current IQ in individuals at familial risk for bipolar disorder is less clear. Cognitive deficits have been associated with genetic risk for bipolar disorder (69,70). One

study showed that siblings of patients with bipolar disorder had lower IQ but that they did not differ on educational level compared with control subjects (71). In contrast, a bipolar twin study showed that both the proband and the co-twin without bipolar disorder completed significantly fewer years of education than control twins (72). Furthermore, population studies show that premorbid IQ or educational attainment are often not affected or are even higher in individuals who later develop bipolar disorder (73–76), whereas IQ during childhood and adolescence is lower in individuals who develop schizophrenia later in life (77–82). The question remains how these measures interact with brain development in individuals at familial risk. As recently reported in a study that included only FDRs-SZ from one site (Utrecht, The Netherlands), current IQ was intertwined with most of the brain abnormalities (15). However, in FDRs-BD, it still remains unclear how IQ and risk for bipolar disorder act on the brain. In the current study, few cohorts had information available on parental SES or subjects' IQ, thereby excluding the possibility to address these variables as potential confounders. Investigating the influence of current IQ on the difference in brain measures between relatives and control subjects was outside the scope of this study, and we are collecting and harmonizing these data from the cohorts for future analysis.

In conclusion, FDRs of patients with schizophrenia or bipolar disorder represent a group of individuals who can provide insight into the effect of familial risk on the brain. Although liability for schizophrenia and bipolar disorder overlap in the general populations, individuals at familial risk assessed here showed a differential pattern of structural brain abnormalities. This study found differences in brain abnormalities between FDRs-SZ and FDRs-BD, in particular, a divergent effect in ICV. This converse effect on ICV suggests that there may be different neurodevelopmental trajectories for each disorder early in life. Taken together, our findings may imply that brain abnormalities in schizophrenia and bipolar disorder are due to genetic variants or gene-by-environment interplay specific to each disorder.

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