Biological Psychiatry: Celebrating 50 Years

Population-Based Mapping of Polygenic Risk for Schizophrenia on the Human Brain: New Opportunities to Capture the Dimensional Aspects of Severe Mental Disorders

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Schizophrenia remains one of the major enigmas in modern biomedicine. The lack of knowledge about disease mechanisms has hampered the development of preventive strategies and more efficient treatment regimens. However, recent progress in psychiatric genetics has provided new hope. The Psychiatric Genomics Consortium has facilitated a series of genetic discoveries, and the most recent schizophrenia genome-wide association study identified 145 genetic loci (1), each with a small effect. Schizophrenia is now established as a polygenic disorder, and it is estimated that 8300 genomic variants are involved (2), calling for new research approaches.

Technological development has also revolutionized brain imaging, and recent studies have exploited unprecedented sample sizes and determined brain magnetic resonance imaging (MRI) abnormalities associated with schizophrenia (3–5). Albeit with a substantial heterogeneity between patients (6,7), the emerging consensus is that schizophrenia, at the group level, is associated with subtle structural differences, such as a thinner cerebral cortex, in particular encompassing frontotemporal brain regions, and smaller subcortical volumes across many regions of the brain—implicating the hippocampus and the cerebellum, among other structures. Recently, the availability of large datasets through global collaborations such as the Enhancing Neuro Imaging Genetics through Meta Analysis (ENIGMA) Consortium and through massive-scale phenotyping and data sharing through the UK Biobank has provided the statistical power needed to start charting the population-based genetic architecture of structural brain MRI measures. Although the field is still maturing, with increasing sample sizes and advances within analytical tools, studies have indicated overlapping polygenic risk factors between schizophrenia and brain imaging abnormalities (7,8). Therefore, polygenic approaches in imaging genetics seem to be a promising path for the discovery of brain mechanisms in schizophrenia.

In this issue of *Biological Psychiatry*, Neilson *et al.* (9) report intriguing findings of a polygenic investigation of brain MRI data in a population-based sample (n = 2864 adults) from the UK Biobank. In addition to investigating associations between individual-level polygenic risk score (PRS) for schizophrenia and birth weight, they tested for associations with sensitive measures of MRI-based brain morphometry, including cortical volume, surface area, and cortical thickness. The results revealed a significant negative correlation between PRS and global cortical thickness, and thickness in the insular lobe, indicating a thinner cortex in individuals with higher PRS for schizophrenia, with small effect sizes. In contrast, they did not find any significant association between schizophrenia PRS and cortical volume or surface area, nor with birth weight.

The Neilson *et al.* study (9) is of great interest for at least two reasons. First, Neilson *et al.* (9) nicely apply schizophrenia PRS to a large MRI sample from the UK Biobank, using data generated from genetics consortia. Second, they report an intriguing association with MRI-based cortical thickness in the general population, suggesting that the effects of high PRS for schizophrenia may influence brain structure in healthy adults. The findings are also of considerable interest because they are highly consistent with a recent report (7), where we applied a similar approach to data obtained from 12,490 healthy individuals in the UK Biobank. We found that a higher PRS for schizophrenia was associated with thinner frontal and temporal cortices, which are brain regions that have consistently been implicated as cortical hotspots in schizophrenia case-control comparisons of MRI-based cortical thickness (3,5). Such neuroanatomical correspondence between the impact of case-control status of a disorder and its PRS in non-symptomatic individuals supports the idea that polygenic approaches are sensitive to biological properties that may be relevant for understanding individual differences in mental and cognitive traits in the absence of a diagnosis.

Mirrored by the recent revolution in psychiatric genetics spearheaded by the Psychiatric Genomics Consortium, the success of imaging genetics depends on the availability of large datasets and statistical power. Although impressive when compared with most previous studies and current standards, the sample size used by Neilson *et al.* (9) is still small given the expected small effect sizes observed in genetics, increasing the chance of false discoveries or null findings. Thanks to the continuous increase in UK Biobank imaging genetics sample size, we are able to empirically address this question. We performed a reanalysis of the effects reported by Neilson *et al.* (9) using the substantially larger sample by Alnæs *et al.* (7) and simulated results using subsets of data. We drew random subsamples from all the 12,490 individuals, with sizes n = 3000 up to n = 12,000 in steps of n = 1000, and resampled and analyzed the individuals in each subsample step 5000 times. We also generated an empirical null distribution by randomly permuting the PRS and recalculating the statistic across 5000 permutations for each sample size.

SEE CORRESPONDING ARTICLE ON PAGE 536

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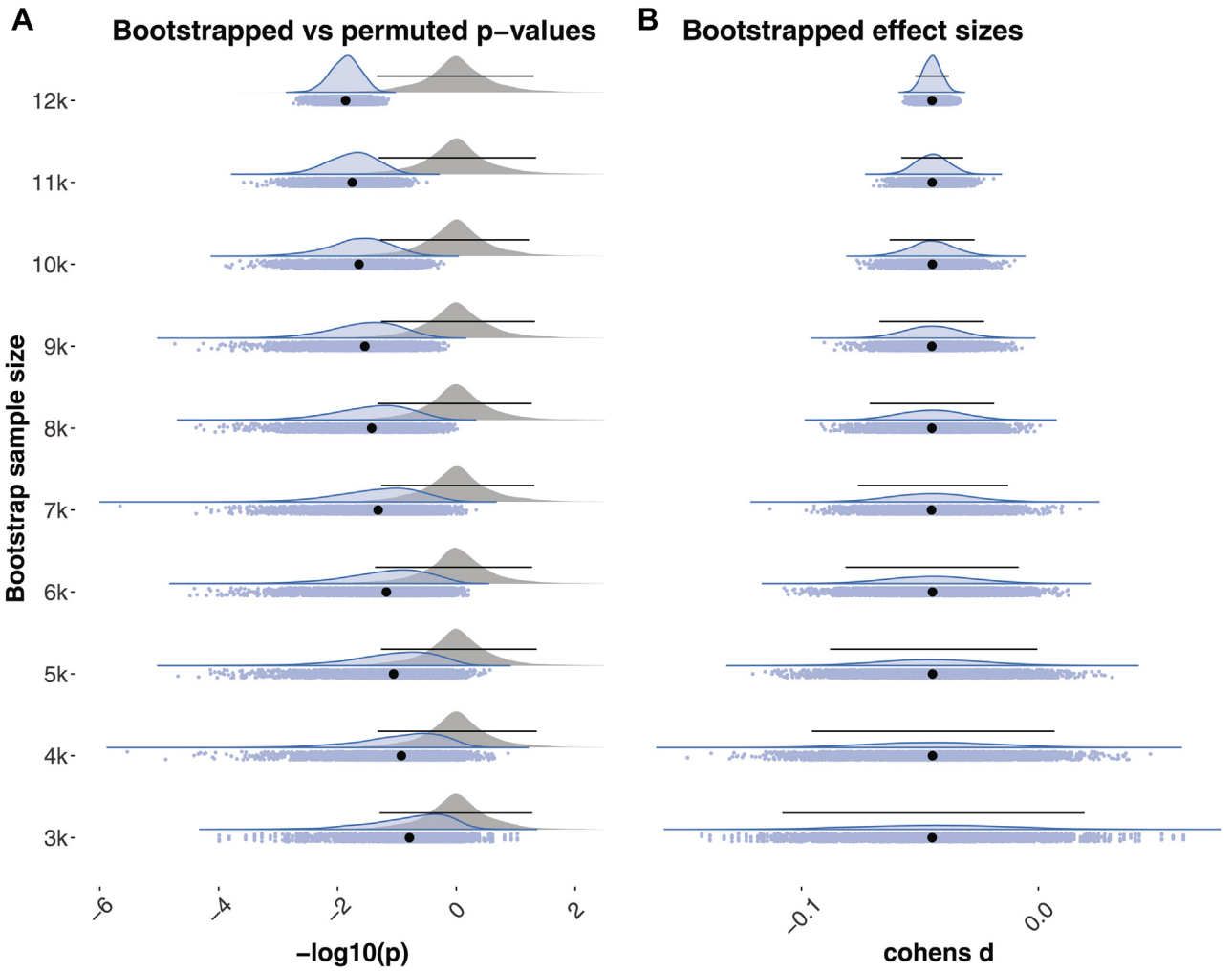

Figure 1. Distributions show bootstrapped associations between schizophrenia polygenic risk score and global cortical thickness for different sample sizes (y-axis). The black dots and lines represent the mean and percentiles (2.5–97.5%) of the empirical distributions. **(A)** Statistical significance (permuted *p* value) for the bootstrapped samples (n = 5000). The permutation distribution (n = 5000) is shown in gray. **(B)** Effect sizes for the associations between polygenic risk score and global cortical thickness.

Our results (Figure 1) suggest that the association between schizophrenia PRS and global cortical thickness converges with a relatively small effect size (Cohen's $d \approx 0.05$). Whereas the grand mean of the point estimates across the 5000 bootstraps converges already at the smallest sample size (n = 3000), the uncertainty of the point estimates decreases with increasing sample size, as expected (Figure 1B). Interestingly, the distributions of the effect sizes from the resampling also demonstrate that the strongest effect size point estimates are more likely to be found among the relatively small sample size analyses than the better-powered larger sample size analyses. This emphasizes that smaller studies not only are more prone to false negatives but also are more prone to false positives with apparent stronger effects (i.e., the winner's curse) than better-powered studies. In addition, the distribution in the observed data can only be clearly discriminated from the empirical null distribution based on permutation testing in the analysis with larger sample sizes ($n > 9000$), demonstrating not only the reduced uncertainty of the estimates but also the increased power to detect small group differences. Together, these reanalyses and simulations support the results from Neilson *et al.* (9) of a subtle negative correlation between global cortical thickness and schizophrenia PRS. In addition, the findings may act as a reminder of the importance and relevance of large datasets in imaging genetics. Combining clinical and dimensional approaches with imaging genetics may therefore be a particularly promising approach to disentangle primary or causal (e.g., genetic or neurodevelopmental) and secondary (e.g., lifestyle factors or medication) effects on the brain in patients with severe mental disorders.

It is thought provoking that PRS of schizophrenia—i.e., the cumulative and joint signal of thousands of sequence variants, each with a tiny effect on the disease phenotype—can have an effect in the healthy population. Given the early stages of research in polygenic underpinnings of schizophrenia and their role in brain MRI measures of brain variation,

we need to be cautious. However, this observation suggests that subtypes of schizophrenia not primarily caused by rare variants (copy number variations, etc.) may be conceptualized as extremes of normal distribution of human traits, in line with theories of schizophrenia pathology and Farley's hypothesis (10) that symptoms in schizophrenia reflect extreme variants of otherwise adaptive social skills and responses.

The relatively subtle and anatomically widespread group differences usually observed in well-powered brain MRI case-control studies (3–5) largely mirror the converging findings from psychiatric genetics that schizophrenia is associated with a large number of genetic variants, each with a small effect. Therefore, the genetic and imaging literature converge on the common notion that schizophrenia (and likely most other mental disorders) is a complex trait with a heterogeneous etiology involving a diverse set of brain phenotypes. Consequently, PRS defined using summary statistics from a large-scale genome-wide association study will pick up any variance reflected in the genome that may be different between cases and controls. Although this has been a highly successful approach for identifying novel variants associated with mental disorders, it also comes with limitations. For example, even subtle group differences in recruitment approaches, exclusion criteria, stratification, comorbidity, etc., are likely to influence and bias the results of the genome-wide association study—and therefore also the PRS derived from the results. Beyond such common design-related challenges, psychiatric disorders defined using current diagnostic criteria do not represent natural kinds, and the current psychiatric nosology does not necessarily comply with biology. Future refinement of the diagnostic categories using biologically informed data may increase specificity both at the genetic level and at the imaging level, with the potential for better clinical impact of these technologies. Future studies including a wider age range than the middle-aged and elderly UK Biobank participants may be able to inform current models of the neurodevelopmental and lifespan dynamics of genetic risk, and further strengthening of global collaborative efforts is needed to assess the generalizability of the findings beyond white Europeans and to establish a truly global science of psychiatric imaging and genetics.

These challenges notwithstanding, the current potential of big data from imaging genetics in elucidating the pathophysiology of schizophrenia and other mental disorders is tremendous. We strongly support the excellent work and open access policy implemented by the UK Biobank, which has revolutionized the scientific approach in many laboratories, including ours. We welcome the intriguing work from Neilson *et al.* (9) and are enthusiastically looking forward to the discoveries obtained from the additional use of large-scale samples in the field of brain imaging and genetics.

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Article Information

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