

The interplay between genetics, cognition and schizophrenia

This scientific commentary refers to ‘Polygenic risk score increases schizophrenia liability through cognition-relevant pathways’, by Touloupoulou et al. 2019.

Schizophrenia is a severe mental disorder with a lifetime prevalence of 6.35 per 1000 (Moreno-Küstner *et al.*, 2018). Multiple treatments are available including antipsychotic drugs, psychological therapies and rehabilitation interventions. Although disease and treatment mechanisms are not fully understood, there is compelling evidence that schizophrenia is highly heritable with around 80% of its variance explained by genetic factors (Hilker *et al.*, 2017). A mega-analysis of genome-wide association studies (GWAS) conducted by the Psychiatric Genomics Consortium identified more than a hundred genetic loci conferring susceptibility to schizophrenia (Ripke *et al.*, 2014). While each individual single nucleotide polymorphism (SNP) carries only a subtle increase in schizophrenia risk (with odds ratios in the range of 1.1 – 1.2), their combination into a cumulative measure called the polygenic risk score provides a stronger predictor of disease (Purcell *et al.*, 2009). In this issue of *Brain*, Touloupoulou and co-workers explore the extent to which impairments in cognition mediate the influence of the polygenic risk score on schizophrenia liability (Touloupoulou *et al.*, 2019).

One approach to identifying the mechanism(s) by which genes predispose to the development of psychotic symptoms is to examine the relationship between the polygenic risk score and endophenotypes – biomarkers of brain structure or function characterising a disease. Deficits in global cognitive ability as well as in specific domains of working memory, attention, and executive function are associated with schizophrenia and have been consistently identified as endophenotypes. Several studies have shown that these cognitive deficits are heritable and are also present in unaffected family members at a higher rate than in the general population. Lencz *et al.* showed in a large study that higher polygenic risk scores for schizophrenia are associated with lower general cognitive ability (Lencz *et al.*, 2014), while Ranlund *et al.* investigated a range of neurophysiological, neuroimaging and cognitive endophenotypes for psychosis and found that higher polygenic risk scores for schizophrenia are associated with poorer spatial visualization skills (Ranlund *et al.*, 2018). Recently, a large genome-wide association mega-analysis of human cognition revealed a bidirectional association with schizophrenia, showing that intelligence has a strong protective effect on schizophrenia risk (Savage *et al.*, 2018).

Even if these studies demonstrate the existence of a genetic overlap between schizophrenia and cognitive deficits, they do not address the direction of causation. Touloupoulou *et al.* therefore set out to explore whether (and to what extent) cognitive impairments mediate the influence of schizophrenia polygenic risk scores on the disorder, or whether the cognitive deficits are instead a consequence of disease progression. They used causal modelling to analyse 1,313 members of 1,078 families (416 people with schizophrenia, 290 of their unaffected siblings, and 607 healthy controls) who volunteered for extensive assessments of global intelligence and specific cognitive skills, as well as genotyping.

Touloupoulou and colleagues confirmed previous findings that the polygenic risk score alone can explain around 8% of inter-individual variation in schizophrenia risk (Ripke *et al.*, 2014; Calafato *et al.*, 2018). More than a third (2.7%) of this polygenic risk score influence is mediated through cognition-related pathways. Furthermore, almost 27% of the genetic liability to schizophrenia is associated with cognition-related pathways not captured by the polygenic risk score. Overall, Touloupoulou *et al.* estimate that around a third (34%) of the genetic risk of developing schizophrenia is mediated by

influences on cognition. Despite cognitive impairments consistently being identified in people with schizophrenia as well as in their unaffected relatives, the underlying pathophysiology remains to be explained. Cognitive deficits alone are probably not sufficient to lead to the development of psychotic symptoms. Other factors, both genetic and/or environmental, are involved, with cannabis use, obstetric complications, malnutrition, childhood maltreatment, trauma, migration and urbanicity some of the best studied environmental risk factors.

Although only a modest 7% to 9% of schizophrenia genetic variance is explained by the polygenic risk score, the score is notable for its ability to capture individual genetic liability in a single quantitative variable (Ripke *et al.*, 2014; Calafato *et al.*, 2018). As the costs of genotyping blood or saliva samples have reduced dramatically, the polygenic risk score is increasingly used to incorporate molecular data into large cohort studies and other experimental designs. There is also growing interest in developing the polygenic risk score as a screening tool, one that may facilitate prompt access to treatment (Purcell *et al.*, 2009; Wray *et al.*, 2014).

While heritability estimates for schizophrenia from twin, family, adoption and other epidemiological studies range from 60% to 80%, the estimates obtained from genome-wide association studies are only about 25% (Hilker *et al.*, 2017; Anttila *et al.*, 2018). This discrepancy, known as schizophrenia's "missing heritability", is attributed to as yet undiscovered common genetic variants as well as to rare genetic mutations and copy number variants (Wray *et al.*, 2014). Indeed, a large exome sequencing study of 12,332 individuals, including 4,877 with schizophrenia, found that putatively protein-damaging rare variants were more abundant in individuals with schizophrenia compared to controls (Genovese *et al.*, 2016). Similarly, a recent analysis conducted by the Psychiatric Genomics Consortium (36,573 schizophrenia cases and 112,468 controls) identified eight regions harbouring rare copy number variants conveying large odds ratios for schizophrenia (Marshall *et al.*, 2017). Further studies using even larger samples are still needed if we are to capture more of the elusive heritability of schizophrenia, and uncover complex gene-environment interactions.

By modelling molecular genetic data captured by polygenic risk scores from families – in which unaffected relatives share genetic and cognitive traits with affected individuals – Touloupoulou *et al.* infer causal relationships between cognition and schizophrenia. Using causal modelling, they convincingly show that a third of the genetic influence on schizophrenia risk is mediated by cognitive pathways and that cognitive deficits are not just an epiphenomenon of the disease. However, since the data available for modelling come from cross-sectional observations, they cannot absolutely prove causality. The timing and severity of any cognitive deficits and whether they are present before and/or after disease onset are key elements in establishing potentially complex cause-effect relationships. Further evidence is needed to corroborate their findings – ideally cohort studies with genomics and multiple prospective, longitudinal cognitive assessments before and after the onset of psychotic symptoms – and to disentangle the relationship between genetics, cognition and schizophrenia.

The polygenic risk scores used by Touloupoulou and colleagues in this study were calculated based on the latest available data from the Psychiatric Genomics Consortium. As the consortium expands this invaluable dataset, the largest international collaboration in mental health, the performance of the polygenic risk scores will be further enhanced. In the near future, we can expect to explain a larger proportion of schizophrenia's genetic liability and the extent to which it is mediated through cognition. Finally, endophenotypes such as cognition offer a unique opportunity to tackle the disease pathway both from research as well as treatment perspectives. Gaining a better understanding of the mechanisms

leading from genes to the development of psychosis is key to developing new therapeutic interventions.

GLOSSARY

Endophenotype: A biomarker or alternative phenotype meeting a number of criteria: It is heritable, associated with an illness but state-independent (manifests whether or not the illness is active), cosegregates with the illness in families, and is found in cases as well as their unaffected family members at a higher rate than in the general population. Endophenotypes are usually quantitative traits (Gottesman and Gould, 2003).

The Psychiatric Genomics Consortium (PGC): A large international collaboration undertaking mega-analyses of genome-wide association studies for a wide range of mental disorders (<http://www.med.unc.edu/pgc>).

Polygenic Risk Score (PRS): A weighted sum of the number of risk alleles carried by an individual. The risk alleles and their effect sizes (the weights) are calculated from an independent sample. In the study by Toulopoulou *et al.*, the PRS is a cumulative measure of genetic liability for schizophrenia obtained from multiple loci. It was calculated using a panel of single nucleotide polymorphisms (SNPs) where each SNP is weighted by the number of risk alleles (0, 1 or 2) a participant carries and by the log of the odds ratio for disease risk obtained from a large and non-overlapping “training” dataset from the Psychiatric Genomics Consortium.

Causal modelling: Mathematical models representing causal relationships within an individual system or population. They facilitate inferences about causal relationships from statistical data, and can help investigate the relationship between probability and causation.

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AUTHORS

Maria Stella Calafato and Elvira Bramon

Neuroscience in Mental Health Research Department, Division of Psychiatry, University College London, UK.

Correspondence to: Maria Stella Calafato E-mail: m.calafato@ucl.ac.uk

FIGURE 1 BELOW

Figure 1: Proposed model whereby genetic and environmental factors influence schizophrenia risk in part through effects on cognition. By modelling both molecular and phenotypic data from families, Toulopoulou *et al.* show that cognition is an important mediator trait (endophenotype) that lies between known genetic factors captured by polygenic risk scores and the disease and that cognition can explain about a third of the known polygenic risk liability for schizophrenia. Environmental and genetic factors also influence schizophrenia risk through alternative cognitive-independent pathways.

