gp.genomicpress.com

Genomic Psychiatry

OPEN

THOUGHT LEADERS INVITED REVIEW

The genetics of cognition in schizophrenia

Michael J. Owen[1], and Michael C. O'Donovan[1]

This conceptual review focuses on recent insights into the nature of the relationship between genetic predisposition and cognitive impairment as risk factors for schizophrenia, and the factors that influence the degree of cognitive impairment in those with the disorder. There is clear evidence that premorbid cognitive impairment is frequently present in those who develop schizophrenia, and, across the range of abilities, poorer premorbid cognition is associated with higher liability to the disorder. Evidence from genetic and population studies strongly supports the hypothesis that premorbid cognitive impairment is a marker for underlying neurodevelopmental risk factors for the disorder, rather than a prodromal manifestation. The premorbid cognitive deficit seems to be largely explained by non-familial factors rather than by familial factors that jointly influence liability to schizophrenia and cognitive ability, and these non-familial risk factors appear act to sensitize individuals to familial risk. There is also evidence that neurodevelopmental risk may be better indexed by the degree to which premorbid cognitive ability deviates from familial expectations than by cognitive ability *per se*. Premorbid cognitive impairment thus does not itself lie on the causal pathway to schizophrenia, rather it is a marker of a neurodevelopmental abnormality that is substantially non-familial, and which increases risk for schizophrenia. Genetic risk factors, including both common and rare alleles, that influence IQ in the general population also contribute both to liability for schizophrenia and to the degree of cognitive impairment in those with the disorder. There is also evidence for further decline in cognitive function after diagnosis in some individuals as well as an increased risk of dementia. This does not appear to reflect substantial shared heritability with neurodegenerative disorders, but the causes of postonset cognitive decline and its relationship to schizophrenia pathophysiology remain uncertain.

Genomic Psychiatry (2024), 1–8; doi: https://doi.org/10.61373/gp024i.0040; Published online: 16 July 2024.

Keywords: Cognition, genetics, genomics, neurodevelopment, schizophrenia

Introduction: Cognitive Impairment in Schizophrenia

Schizophrenia is diagnosed based on the presence of core positive (psychotic), negative and disorganized symptoms (1). Individuals meeting diagnostic criteria show considerable heterogeneity in these and other clinical features, as well as in course and outcome (2). Comparisons between people with schizophrenia and controls reveal groupwise impairments in most aspects of cognitive function (3, 4) including IQ, which is on average reduced by approximately 1 SD in cases (5). Again, there is enormous variation between individuals in the extent of the impairment present, and a diagnosis of schizophrenia does not preclude estimates of cognitive ability that are above, and sometimes markedly above, average (6, 7). Cognitive impairment is not a core symptom of schizophrenia in DSM5 or ICD11, but as it is strongly associated with poorer functional outcomes in areas such as work, independent living, and social integration (3), it is of great importance to those with the disorder, and to those who are involved in their care and management, A recent review has broadly considered evidence concerning the etiology, pathogenesis, and treatment of cognitive impairment in schizophrenia (4). The current conceptual review is more circumscribed and focuses on additional important insights provided by recent studies into the nature of the relationship between genetic risk and cognitive impairment as risk factors for schizophrenia, and the factors that influence the degree of cognitive impairment in those with the disorder.

Many of the studies we review have been based upon derived measures of general cognitive function such as IQ rather than upon performance on specific tests measuring specific domains of cognitive function. Given that impairments in most aspects of cognitive function are associated with schizophrenia (3), we believe that such global measures are informative for the specific questions we aim to address. Accordingly, we use the term cognitive impairment interchangeably with low IQ rather than to indicate impairment in specific cognitive domains.

People who receive a diagnosis of schizophrenia frequently exhibit "premorbid" cognitive impairments before psychosis is manifest (8), including an average IQ that is approximately 0.5 SD below that of controls (5). There is also evidence that the severity of premorbid impairment is associated with earlier onset of schizophrenia (9). Impairments are evident in childhood (5, 10–12) and appear to represent a failure of typical developmental acquisition of function rather than a deterioration *per se* as might be expected of a degenerative process (12). While the evidence suggests that the developmental trajectories of those who develop schizophrenia diverge from controls many years before psychosis emerges, it remains unclear whether this is preceded by a period of normal development and, if so, exactly when divergence begins (10, 12). Alongside other premorbid developmental and environmental risk factors, the findings point to schizophrenia having origins in disturbances of neurodevelopment, one manifestation of which is impaired cognition prior to onset of psychosis (13–15).

While the weight of evidence supports a neurodevelopmental explanation for premorbid cognitive impairment in schizophrenia, the nature of the relationship between the two is uncertain. In principle, there are three possibilities. First, premorbid cognitive impairment could be a prodromal manifestation of an insidious onset of schizophrenia. Secondly, it could be a causal risk factor mediating the effects of genetic or environmental risk on the development of schizophrenia, a so-called intermediate phenotype or endophenotype. Thirdly, it might be a risk indicator that results from the pleiotropic effects of an underlying neurodevelopmental abnormality that independently increases risk of the subsequent emergence of schizophrenia. In this latter instance, premorbid cognitive impairment would be a marker of the presence or extent of a neurodevelopmental abnormality but not itself lie on the causal pathway to schizophrenia.

Some studies comparing cognitive function in the same individuals before and after onset of schizophrenia (5, 16–18) suggest that, as well

[1]The Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, and Neuroscience and Mental Health Innovation Institute, Hadyn Ellis Building, Maindy Road, Cardiff University, Cardiff CF14 4HQ, UK.

Corresponding Author: Michael J. Owen, Hadyn Ellis Building, Maindy Road, Cardiff University, Cardiff, UK, CF14 4HQ. E-mail: owenmj@cardiff.ac.uk

Received: 26 April 2024. Revised: 19 June 2024. Accepted: 19 June 2024.

as premorbid deficits, there is further decline in function after diagnosis in some individuals. However, this remains a controversial area and two meta-analyses of longitudinal studies found no evidence for postonset decline in the first 5 years after onset (19, 20). Moreover, a recent umbrella review concluded that most of the reviews assessed point to no decline of cognitive function over short to medium time frames (21). Nevertheless, studies over longer follow-up periods have found evidence for accelerated cognitive decline (18) and substantially increased risks of dementia have been reported in those with schizophrenia (22, 23). Some have argued that this later decline points to the operation of a primary neurodegenerative process in schizophrenia (24), whereas others have argued that many people with schizophrenia do not progressively deteriorate and pointed to the possibility that, where decline does occur, it reflects non-specific factors secondary to schizophrenia such as antipsychotic exposure, metabolic syndrome, smoking and other substance abuse and various social confounders (25, 26).

Finally, the considerable variation in cognitive impairment seen in people with schizophrenia raises the question as to what extent this might be associated with the same genetic factors that influence variation in cognitive ability in the general population, or whether factors that are relatively specific to schizophrenia operate.

Genetic Architectures of Schizophrenia and Intelligence

Schizophrenia is highly heritable and polygenic, with risk conferred by alleles across the frequency spectrum (27). Genome-wide association studies have so far identified 287 loci that contain common risk alleles of small effect (28), but many more exist, likely thousands, that are collectively responsible for around a third of genetic liability (29, 30). In addition, at least eight rare copy-number variants (CNVs) have been identified that confer substantial individual risk (31, 32). More recently, exome sequencing studies have shown rare protein truncating variants and damaging missense mutations (33–39) can confer large effects on risk of schizophrenia. The largest exome wide sequencing study of the disorder to date reported by the Schizophrenia Exome Meta-Analysis Consortium (SCHEMA) (38) identified 10 genes with an exome-wide significant excess burden of these classes of mutation in cases. An additional two genes met this significance threshold in a focused sequencing study targeting genes that had shown some evidence for association in a preliminary analysis of the SCHEMA exome wide study (40).

Genomic studies of common variants have found evidence for genetic correlation between schizophrenia and other psychiatric conditions and personality traits, with the strongest relationship seen with bipolar disorder where the shared heritability is approximately 0.7 (41). In contrast, for rare variants, while there is evidence for overlaps with bipolar disorder (42), so far, the genetic overlaps are more prominent between schizophrenia and childhood onset neurodevelopmental disorders (NDDs) which, like schizophrenia, are also associated with cognitive impairment: all known schizophrenia associated CNVs have been implicated in intellectual disability, and some have also been implicated in autism (43). People with schizophrenia are also enriched for ultra-rare damaging mutations in NDD-associated genes (33, 36–39), including specific mutations that are pathogenic for NDDs (44). Finally, common schizophrenia risk alleles are enriched in genes implicated by rare variant studies of NDDs (28).

Intelligence is moderately heritable in the general population (45). Genomic studies have shown that, like schizophrenia and as predicted (45), it is highly polygenic, and impacted by alleles across the frequency spectrum including many common variants of small effect (46), as well as rare alleles including chromosomal abnormalities, CNVs, and rare coding variants, some of which are also associated with schizophrenia and other NDDs (47–50).

The Relationship Between Genetic Risk and Cognitive Impairment as Risk Factors for Schizophrenia

Family and Population Studies

There is evidence from many individual studies, supported by meta-analyses, that unaffected first-degree relatives (FDRs) of those with schizophrenia show generalized impairments of cognitive function but to a lesser degree than those seen in probands (51, 52). However, such findings are not universal. One study of schizophrenia cases and their relatives from relatively highly functioning families found that the siblings of probands did not differ in cognitive performance from a community control sample (53). In addition, a very large study of the Swedish population found no evidence for adolescent cognitive impairment in the siblings of people with schizophrenia (54). These findings raise the possibility that the role of familial risk factors for low IQ in schizophrenia may have been influenced by ascertainment bias in studies of probands and their relatives. Another possible confounder is that families ascertained for having a schizophrenia proband may have higher rates of exposure to environments with an impact on cognitive ability, for example cannabis abuse (55). Finally, there is evidence for assortative mating such that people with schizophrenia who have children on average have partners of lower cognitive ability than controls (56). As a result, assortative mating could contribute to, or even account for, deficits in FDRs rather than these reflecting a substantial overlap between the genetic risk for schizophrenia and low IQ. Thus, while many studies have found evidence for impaired cognition in FDRs, questions remain about how these findings should be interpreted. Genomic studies of parent-proband trios might throw light on this issue.

Population studies have further illuminated the causal relationship between premorbid IQ and genetic risk. In a large study of the Swedish population (57), risk of schizophrenia increased by 3.8% with each one-point decrease in premorbid IQ. The effects were stronger in the lower IQ range, but importantly, the association was monotonic, meaning at no point in the distribution was higher IQ associated with higher risk, although such an effect in people with exceptionally high IQ could not be excluded due to the rarity of those individuals. Overall, these findings, and the magnitude of the effect, were almost identical to those obtained in a meta-analysis of earlier population studies (9). The Swedish study (57) noted that the association between premorbid IQ and risk of schizophrenia was of similar magnitude when onsets within 5 years of testing were excluded, suggesting that it does not reflect potential prodromal effects of declining IQ associated with insidious onset. Again, these findings are in accord with those from earlier population studies which excluded onsets immediately prior to testing (51). Finally, the Swedish study found that that risk of schizophrenia in people with high familial liability to the disorder was substantially modified by premorbid IQ, familial susceptibility having a much stronger impact on risk of illness in those with low IQ.

Since intelligence and schizophrenia are both familial and substantially heritable, the authors of the Swedish study (57) tested the hypothesis that the premorbid IQ-schizophrenia association might be the result of genetic (and family environment) factors that predispose to both traits. They undertook co-relative analyses, comparing the strength of the association between intelligence and schizophrenia within various classes of pairs of relatives whose IQs were different, that is not in the same decile. Siblings share more familial factors (genetic and environmental) than do more distal pairs of relatives, and therefore more of the difference in intelligence between them is likely to be attributable to non-familial factors than is the case for difference in intelligence between more distally related pairs. Accordingly, if the association between low IQ and schizophrenia is substantially due to genes or familial environments that influence both traits, the strength of this association within siblings will be less than in the more distantly related relative pairs. However, the findings were inconsistent with this; association between premorbid IQ and schizophrenia was as strong within siblings as within more distant relatives, and even between people in the general population who are effectively unrelated, suggesting the link between the traits is not the result of heritable genetic or familial environmental risk factors that jointly influence both traits. These findings have been supported by two recent population-based sibling studies (58, 59).

Evidence that non-familial factors may have an important influence on premorbid IQ deficits in schizophrenia also comes from studies showing that risk of schizophrenia may be better indexed by a measure of the extent to which an individual's premorbid cognitive performance is lower than expected based on estimates of familial cognitive aptitude than by their absolute premorbid cognitive performance *per se* (54, 60, 61). It is conceivable that such deviations from familial expectation might occur

in individuals who, by an unlucky roll of the genetic dice, inherit an excess of poorer cognition alleles that have pleiotropic effects on liability to schizophrenia. However, this interpretation was not supported by the finding that, when schizophrenia and control probands were matched for cognitive performance, the siblings of the schizophrenia probands had scholastic aptitudes and IQs that did not differ from population means and which were significantly higher than those of the siblings of control probands (54). Instead, this series of studies from Sweden (54, 57, 60) suggest that an important contribution to risk for schizophrenia comes from neurodevelopmental perturbations that impact cognitive development in people who develop schizophrenia that are not caused by familial factors that typically influence cognition within families. This general conclusion also is indirectly supported by evidence that the heritabilities of a range of cognitive abilities in schizophrenia seem to be lower than in the general population (61).

Overlap in Common Risk Alleles for Schizophrenia and IQ

There is evidence that some of the common alleles that influence cognitive ability in the general adult population also influence liability to schizophrenia, but the genetic correlation of −0.21 between the two is modest (46). A similar genetic correlation of −0.22 has also been reported between liability to schizophrenia and intelligence estimated in 16 year olds, an age prior to the typical onset of schizophrenia (62). These correlations suggest that, on average, common variant genetic effects associated with lower intelligence in the general population explain around 5% of liability to schizophrenia, an estimate consistent with a longitudinal population-based twin study which estimated this figure at 7% (63). These findings, based on very different study designs, converge on the conclusion that, while there is some shared genetic liability between IQ and risk of schizophrenia, the overlap is small, and in line with the conclusions from the Swedish family studies reviewed above. It should be noted that genetic correlations of this magnitude could potentially be the result of the type of cross-trait assortative mating (64) discussed above (56), as well as other sources of confounding (65), possibilities that warrant further study. Moreover, shared liability does not imply that risk of schizophrenia is mediated by the effects on cognitive ability, it may instead indicate the existence of pleiotropy whereby common alleles independently influence cognitive ability and liability to schizophrenia, perhaps by contributing to the pleiotropic neurodevelopmental perturbations discussed in the previous section.

A study (66) based on modeling the relationships between schizophrenia polygenic liability [indexed by polygenic risk score (PRS)], schizophrenia and cognition (expressed as latent traits) within families found that the best model solutions suggested around a third of genetic risk of schizophrenia could be explained through causal effects on cognition. However, the modeling does not appear to have accounted for the possibility of pleiotropy, and, as the authors noted, the limitations and assumptions mean that their approach cannot prove causality, and longitudinal designs and/or Mendelian randomization approaches are needed. However, to date, the required longitudinal studies have not been conducted and Mendelian randomization methods have not been able to clearly distinguish between causal and pleiotropic hypotheses (67). Moreover, a recent report that almost all variant sites that influence IQ in the general population also influence liability to schizophrenia, but that the specific alleles that increase schizophrenia risk are a mix of lower and higher IQ alleles, suggests that shared liability cannot indicate a simple causal link between lower IQ *per se*, and schizophrenia (68).

Genomic Studies of Variation in Cognitive Function in Schizophrenia

Common Alleles

Separate to the question about the relationship between alleles that influence cognition in the general population and those that influence liability to schizophrenia is what is the relationship of those sets of alleles to cognitive ability in people with the disorder?

There is strong evidence that alleles influencing IQ in the general population also have effects on cognitive ability in individuals with schizophrenia (69–71). In contrast, the evidence for a relationship between cognitive function in schizophrenia and common variant liability for the disorder is inconsistent (69, 70, 72–75). This inconsistency may reflect the relatively modest sample sizes and power of some of the studies as well as differences in duration of illness at the time of cognitive testing and the nature of the cognitive tests employed. Nevertheless, the results suggest that the effects of common schizophrenia risk alleles, as indexed by a polygenic risk score (PRS), on cognition in people with schizophrenia are at best small, and where direct comparisons have been made (69–71), considerably smaller than the effects of common alleles that influence IQ in the general population (as indexed by an IQ PRS). The IQ PRS explains around 9% of variance in IQ (76) in people with schizophrenia. This is similar to estimates in the general population (62), although one study suggested the variance explained in cases is less than in UK Biobank controls, albeit using different cognitive measures in cases and controls (70). These findings, together with those indicating that the genetic correlation between liability to schizophrenia and IQ is modest, and the findings from the large population family studies reviewed above, suggest that variation in premorbid cognitive function in people who later develop schizophrenia is not substantially the result of common genetic risk factors for schizophrenia. There is also clear evidence from genomic studies that common alleles that influence variance in cognitive ability in the general population also do so in people with the disorder. However, in the absence of direct comparisons of cases and controls based on identical cognitive assessments, it is unclear to what extent those alleles can explain the average premorbid cognitive deficit seen in people who develop schizophrenia.

Rare Variants

People with schizophrenia who carry schizophrenia associated CNVs tend to have worse cognitive function than those do not, the average difference between the two groups in measures of cognitive performance being around 0.5–1.0 SD (77). The greatest reductions in cognitive ability are seen in those with CNVs spanning loss-of-function intolerant (LoFI) genes, that is genes in which loss-of-function mutations are highly disadvantageous for reproductive fitness. There is also evidence that in people with schizophrenia, rare coding risk variants (RCVs), particularly protein-truncating variants in LoFI genes, are associated with reduced cognitive function (71, 76), poorer educational attainment (33, 78) and an increased risk of comorbid intellectual disability (37, 78). The effects of rare variants on cognition are largely manifest before illness onset (see below), suggesting that their effects impact neurodevelopmental processes. Further support for neurodevelopmental effects comes from the observation that the effects of RCVs on cognitive function in schizophrenia are on average greater for those within genes that have been implicated in childhood NDDs than for RCVs in other mutation intolerant genes (37, 76, 78). Given evidence reviewed above that non-familial effects are important, it is also notable that the effect sizes of mutations occurring *de novo* (which by definition are non-familial) are larger than those of transmitted mutations (38, 76, 78).

Premorbid versus Postonset Effects

Few genomic studies have included measures of both premorbid and current cognition in people with schizophrenia, but a small number of recent studies that have done so have begun to throw some light on the links between genetic risk factors and the timing of cognitive impairment. Most of the impacts of CNVs, RCVs, and IQ PRS on cognition are premorbid (69, 71, 76, 77). In contrast, there is some evidence that the relatively small effects of common variant schizophrenia liability on cognition occur after onset (69) but do not influence premorbid cognitive ability (69, 71, 76). The findings that schizophrenia common variant liability, while not associated with premorbid impairment, may be associated with later impairment requires replication, but if confirmed, might either reflect effects on cognitive decline around the time of onset of psychosis or at some point thereafter. The findings from a longitudinal study that association between schizophrenia PRS and poorer cognition is stable across a 20-year follow-up period (75) would tend to suggest that the effects on cognition are most likely to occur around the time of onset.

Regarding the substantial increases in risk of dementia reported in schizophrenia mentioned above, it is notable that there is no evidence that schizophrenia shares heritability with Alzheimer's or Parkinson's

diseases, although there is weak evidence for some sharing with frontotemporal dementia (79–81).

Conclusions and Implications

The findings from genetic studies that we have described are relevant to three broad sets of issues. The first concerns the question of what accounts for the lower premorbid IQ seen in schizophrenia and the nature of the relationship between this impairment and other risk factors for schizophrenia. The second relates to what genetic factors influence the extent of cognitive impairment among those with schizophrenia. The third concerns the possible influence of genetic effects on cognitive decline in later life.

Premorbid Cognitive Impairment and Risk of Schizophrenia

Evidence reviewed above suggests that low premorbid IQ is a risk factor for schizophrenia and that this is not explained by prodromal effects of an insidious onset of the disorder. Moreover, rather than an "U"-shaped relationship between IQ and risk of the disorder, highest risk occurs in people with lowest IQ, lowest risk in those with the highest IQ, and on average, people who subsequently develop schizophrenia have a 0.5 SD deficit in premorbid IQ compared with the general population average.

In principle, the strong evidence that schizophrenia risk alleles can also influence cognitive ability in the general population provides a plausible explanation for low premorbid IQ. Intuitively attractive though this hypothesis may be, it is not supported by the evidence we have discussed. Common variant genetic liability to schizophrenia, which currently explains by far most of the attributable heritability of the disorder (82), does not appear to be associated with premorbid IQ (69, 71), a finding broadly consistent with the small genetic correlations observed between liability to psychosis and premorbid IQ in twins and between schizophrenia and IQ in the general population. Thus, the genomic evidence to date is consistent with that outlined above from genetic epidemiology in suggesting that the premorbid cognitive deficit in schizophrenia is largely explained by non-familial rather than familial factors that jointly influence liability to schizophrenia and cognitive ability. There is strong evidence these non-familial factors include *de novo* mutations (SNVs and CNVs), but these have been implicated in fewer than 5% of cases (82) and therefore other non-familial risk factors must contribute, including as yet unidentified *de novo* mutations, such as rare structural variants and non-coding variants, non-familial environmental factors, for example *in utero* or perinatal birth trauma and infections, and stochastic events (83) that contribute to variation in neurodevelopment.

Some caveats should be noted. First, it is conceivable that studies of the effects of schizophrenia PRS on cognition in cases may underestimate effects due to Berkson's paradox (84), also sometimes known as collider bias (84). Assuming PRS and low IQ to be at least partly independent risk factors, people with exposure to higher PRS will require less exposure to the risk conferred by low IQ in order to manifest the disorder, and vice versa. This can result in a spurious negative correlation between the two risk factors in case only studies, or, where a true population association exists, a reduction in the estimated effect size. Secondly, only a minority of schizophrenia heritability is currently attributable to known types of variant (82) and, in principle, classes of variants responsible for the unexplained heritability could show stronger associations with cognition, although the findings from studies of siblings and other relatives reviewed above (57–59) suggest that this is unlikely to be the case. Thirdly, the findings of the key genetic epidemiological studies require further replication.

Having established that low premorbid IQ is a risk factor for schizophrenia the next question is whether low IQ is *per se* causal or is instead a risk indicator of a pleiotropic neurodevelopmental abnormality that can (largely) independently manifest as low IQ in childhood and the emergence of schizophrenia in later life. The latter interpretation is supported by the observation that risk of schizophrenia is better indexed by the deviation of cognitive performance from that expected, than by absolute premorbid cognitive performance, which is contrary to the expectation if low IQ *per se* is directly causal. Molecular genetic studies of common and rare variation are also inconsistent with the idea that low IQ *per se* is on the causal pathway to schizophrenia. Thus, while all known schizophrenia-associated CNVs, and certain schizophrenia—associated RCVs are associated with low IQ, their impacts on risk in schizophrenia is not contingent on the presence of low IQ (41). The observation that common schizophrenia susceptibility alleles include those associated with higher IQ as well as lower IQ similarly suggests that there is no robust causal link between lower IQ and schizophrenia. There is, however, evidence that low premorbid IQ may sensitize individuals to familial risk factors (57) (Figure 1A) and there is a need to substantiate this finding and, if confirmed, explore possible mechanisms.

A further issue that warrants discussion is whether there is a neurodevelopmental subtype of schizophrenia characterized by premorbid cognitive impairment. We have discussed this elsewhere (44) and our view is that the evidence better supports the hypothesis that there is a spectrum of neurodevelopmental impairment in those with schizophrenia, rather than a clear distinction between a form of the disorder with cognitive impairment and one without (15). The monotonic change in risk of schizophrenia across the full IQ range, rather than there being an IQ threshold that is associated with a step change in liability, supports this (9, 57) as does the observation that people with lower cognitive ability in schizophrenia do not substantially differ from those with higher cognitive ability with respect to common alleles that confer risk to schizophrenia generally (70). Finally, in people with CNVs known to affect neurodevelopment, schizophrenia is the result of both the CNV and the common variant liability that is shared with general forms of the disorder (85, 86). While we do not believe that the data support the existence of a distinct neurodevelopmental subtype of schizophrenia, the extent of premorbid cognitive impairment, and more particularly the extent that this deviates from familial expectations, seems to index the degree of underlying neurodevelopmental impairment and may be an important clinical and prognostic marker within the disorder (Figure 1B).

We additionally note that while our focus here is schizophrenia, comparisons of the degree of premorbid deviation from familial cognitive aptitude (60) in different psychiatric disorders support the view that the neurodevelopmental continuum extends across a number of conditions, as previously proposed (15, 87). Thus, the effect size of deviation from familial cognitive aptitude was greatest for ASD, followed by schizophrenia and other non-affective psychoses, and least in bipolar disorder (60) supporting the suggestion (15, 87) that there is a gradient of neurodevelopmental pathology across neurodevelopmental and psychiatric disorders. According to this view schizophrenia occupies an intermediate position between childhood neurodevelopmental conditions and bipolar disorder. This helps explain why cognitive impairment is associated with schizophrenia but to a much lesser extent bipolar disorder despite the high common variant genetic correlation between the two conditions.

It is now important to identify the risk factors for, and the nature of, the neurodevelopmental abnormality underlying premorbid cognitive impairments.

It will also be important to determine how and when neurodevelopmental impairment moderates the impact of familial genetic risk for schizophrenia. One hypothesis with potential implications for interventions is that the effects of divergence from familial cognitive expectations on psychopathology might be mediated by the evocation of disrupted family dynamics and/or impairment of individual's self-esteem (88) (Figure 1).

Genetic Factors Influencing the Degree of Cognitive Impairment in Schizophrenia

As we have seen, recent genomic studies suggest that all classes of allele that influence liability to schizophrenia or to variance in IQ contribute to variation in premorbid cognition and to cross-sectional degree of cognitive impairment in people with established schizophrenia. These types of variant currently explain around 10% of variance in premorbid IQ, of which, as noted above, 90% is explained by IQ PRS and the remainder by rare CNVs and rare damaging coding variants in constrained genes. They explain less variance in cognition, around 6%, in those with established schizophrenia (76), but after allowing for the effects of premorbid cognition, this drops to around 1.6%, equally split between IQ and schizophrenia PRS. Thus, most of the genetic contribution to variation in cognition in

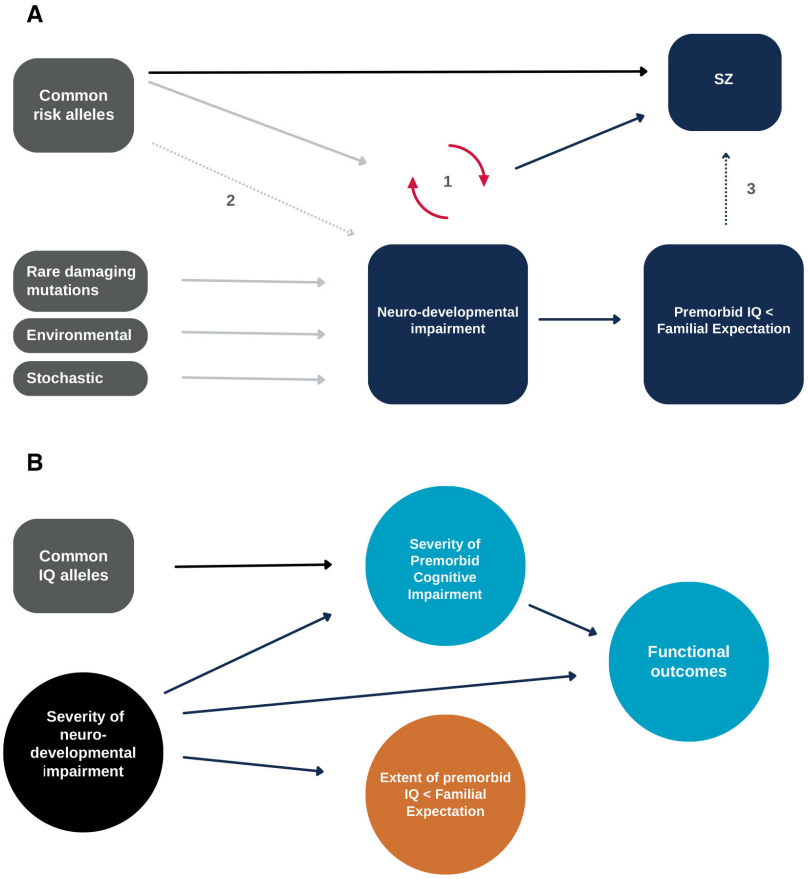

Figure 1. (A) A model of the relationship between premorbid cognitive impairment and risk of schizophrenia. The degree to which premorbid IQ deviates from familial expectations, rather than IQ *per se,* is a key risk indicator for schizophrenia. This deviation indexes an underlying neurodevelopmental impairment (NDI) that increases the risk of schizophrenia, and which sensitizes the individual to familial risk factors including common variant liability indexed by schizophrenia PRS as well as some other forms of transmitted genetic variant (1). The NDI reflects predominantly non-familial factors including environmental risk factors, stochastic factors and rare damaging de novo mutations. However, familial risk of schizophrenia likely contributes to NDI (2) given evidence that genes implicated by common risk variants overlap those associated with rare disruptive coding variants in schizophrenia, are enriched for genes implicated by such variants in NDDs (28) and evidence that they are enriched for genes with high expression specificity in developing fetal neuronal populations independently of those expressed in adulthood (89). An individual's deviation from familial cognitive aptitude expectation might impact on their psychopathology via influences on their self-esteem and family relationships (3). (B) Severity of premorbid cognitive impairment in schizophrenia. The severity of premorbid cognitive impairment in individuals with schizophrenia reflects both the contribution of common alleles that are associated with IQ in the general population indexed by IQ PRS and the severity of the underlying NDI which is indexed by the extent of premorbid cognitive impairment relative to familial expectations. The latter is likely to be an important marker of stratification within the disorder indicating a propensity to poor functional outcomes. The direct arrow from NDI to outcomes acknowledges that more research is needed to determine the extent to which different outcomes are mediated by cognitive impairment.

schizophrenia is mediated by effects that we have argued above are neurodevelopmental. Also note that, while rare mutations contribute only a small amount to variance in premorbid cognition, they are associated with relatively large impairments of cognitive function (76).

A caveat to our conclusion that most of the genetic influences on cognition in schizophrenia are premorbid and likely neurodevelopmental is that, given our incomplete understanding of genetic architecture, we cannot exclude the existence of as yet unknown types of risk variant that show a different balance of morbid and premorbid effects on cognition. The existence of such variants is plausible given evidence we have discussed that any effects on cognition of common risk alleles for schizophrenia seem to manifest postmorbidly rather than premorbidly (69). Another caveat is there may be specific genetic contributions to cognition in schizophrenia that are independent of those that confer liability to the disorder, or to intelligence in the general population.

Genetic Influences on Postonset Cognitive Decline

As we have seen, uncertainties remain concerning the extent to which there is cognitive decline after onset and if so what proportion of cases are affected and when the decline occurs. There is emerging evidence of decline in cognitive function after schizophrenia onset relative to age matched controls, which appears to be progressive over many years (18) and for substantially increased risks of dementia (22, 23). The presence of late life cognitive decline and increased risk of dementia in people with schizophrenia in the absence of increased genetic liability to dementia suggests that schizophrenia may lead to higher exposure, or greater vulnerability, to the same environmental risk factors that operate in the general population to increase risk of dementia, for example smoking, poor cardiovascular health, and lower cognitive reserve, the latter being a consequence of lower premorbid IQ, social isolation, and low rates of employment. A second explanation is that the increased risk of dementia reflects intrinsic pathogenic mechanisms related to schizophrenia, or environmental exposures, that are relatively specific to those with severe mental illness for example medication effects. This is an area that needs further research that includes measures of genetic and potential environmental risk factors and robust measures of cognition ideally over multiple timepoints (24, 26).

Limitations

An important limitation of many of the cited studies is that different measures of cognition have been used and analyses have typically been based upon derived measures of general cognitive function such as IQ rather than upon performance on specific tests measuring specific domains of cognitive function. In defense of this approach, the evidence suggests that reductions in most aspects of cognitive function are associated with schizophrenia (3) in line with an underlying neurodevelopmental impairment that impacts broadly on cognitive performance. However, it is possible that there are specific cognitive impairments that are important mediators of risk that will be identified by future research. Additionally, the measures of premorbid cognitive function used in many genomic studies have been indirect. Concern is mitigated to some extent by studies showing that such measures are strongly correlated with direct measures of premorbid IQ (90). However, we acknowledge that large longitudinal cohorts with direct measures of cognitive function would offer a better means of investigating how genetic and other risk factors influence cognitive function over the lifespan in those with schizophrenia. Finally, as we have noted, only around 10% of variance in cognition in schizophrenia is currently attributable to alleles of the classes so far studied, and even then, the vast majority of this is attributable to polygenic scores rather than specific causal alleles. Our inferences are therefore based on an incomplete understanding of the genetic architecture of cognition in the general population as well as in schizophrenia.

Conclusions

Despite these limitations and the caveats and uncertainties we have noted throughout, the available evidence from genetic studies has allowed us to identify some important conclusions and to propose a model of the relationship between premorbid cognitive impairment and risk of schizophrenia which best fits the current data (Figure 1). This model will no doubt need to be revised as further findings accumulate. In particular, it will be important to further replicate the finding that deviation from familial cognitive aptitude is a better risk indicator than IQ *per se* and to understand the genetic and environmental factors that underlie this deviation and how it interacts with genetic risk for schizophrenia. However, as it stands our model and the data upon which it is based have important implications for interpreting both endophenotype and animal model studies as well as for interventions aimed at improving cognitive function in schizophrenia.

The factors underlying cognitive decline after onset remain unclear and it is not apparent to what extent these are intrinsic to the disease process or secondary to schizophrenia such as antipsychotic exposure, metabolic syndrome, smoking and other substance abuse and various social confounders. Understanding how and when the effects on cognition, premorbid, and postonset, arise are key questions for research given the potential for prevention and early intervention.

Acknowledgments

The work was supported by a Medical Research Council Centre grant MR/L010305/1 and programme grant MR/P005748/1. The content is the responsibility of the authors and does not necessarily represent the official views of the funding bodies. We are grateful to Victoria Hirst for assistance with manuscript preparation, and Catrin Hopkins and Ellie Short for help with the figures.

Author Contributions

M.J.O. and M.C.O. reported receiving grants from Akrivia Health and the Takeda Pharmaceutical Company Ltd outside the submitted work. Takeda and Akrivia played no part in the conception, design, implementation, or interpretation of this study.

References

1. Tandon R, Gaebel W, Barch DM, Bustillo J, Gur RE, Heckers S, et al. Definition and description of schizophrenia in the DSM-5. Schizophr Res. 2013;150(1):3–10. DOI: 10.1016/j.schres.2013.05.028. PMID: 23800613
2. Owen MJ, Sawa A, Mortensen PB. Schizophrenia. Lancet. 2016;388(10039):86–97. DOI: 10.1016/S0140-6736(15)01121-6. PMID: 26777917; PMCID: PMC4940219
3. Green MF, Horan WP, Lee J. Nonsocial and social cognition in schizophrenia: current evidence and future directions. World Psychiatry. 2019;18(2):146–61. DOI: 10.1002/wps.20624. PMID: 31059632; PMCID: PMC6502429
4. McCutcheon RA, Keefe RSE, McGuire PK. Correction: Cognitive impairment in schizophrenia: aetiology, pathophysiology, and treatment. Mol Psychiatry. 2023;28:1919. DOI: 10.1038/s41380-023-01984-6. PMID: 36732589; PMCID: PMC10575768
5. Woodberry KA, Giuliano AJ, Seidman LJ. Premorbid IQ in schizophrenia: a meta-analytic review. Am J Psychiatry. 2008;165(5):579–87. DOI: 10.1176/appi.ajp.2008.07081242. PMID: 18413704
6. Palmer BW, Heaton RK, Paulsen JS, Kuck J, Braff D, Harris MJ, et al. Is it possible to be schizophrenic yet neuropsychologically normal? Neuropsychology. 1997;11(3):437–46. DOI: 10.1037/0894-4105.11.3.437. PMID: 9223148
7. Cernis E, Vassos E, Brebion G, McKenna PJ, Murray RM, David AS, et al. Schizophrenia patients with high intelligence: a clinically distinct sub-type of schizophrenia? Eur Psychiatry. 2015;30(5):628–32. DOI: 10.1016/j.eurpsy.2015.02.007. PMID: 25752725
8. Lewandowski KE, Cohen BM, Ongur D. Evolution of neuropsychological dysfunction during the course of schizophrenia and bipolar disorder. Psychol Med. 2011;41(2):225–41. DOI: 10.1017/S0033291710001042. PMID: 20836900
9. Khandaker GM, Barnett JH, White IR, Jones PB. A quantitative meta-analysis of population-based studies of premorbid intelligence and schizophrenia. Schizophr Res. 2011;132(2-3):220–7. DOI: 10.1016/j.schres.2011.06.017. PMID: 21764562; PMCID: PMC3485562
10. Reichenberg A, Caspi A, Harrington H, Houts R, Keefe RS, Murray RM, et al. Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: a 30-year study. Am J Psychiatry. 2010;167(2):160–9. DOI: 10.1176/appi.ajp.2009.09040574. PMID: 20048021; PMCID: PMC3552325
11. Jones P, Rodgers B, Murray R, Marmot M. Child development risk factors for adult schizophrenia in the British 1946 birth cohort. Lancet. 1994;344(8934):1398–402. DOI: 10.1016/s0140-6736(94)90569-x. PMID: 7968076
12. Mollon J, David AS, Zammit S, Lewis G, Reichenberg A. Course of cognitive development from infancy to early adulthood in the psychosis spectrum. JAMA Psychiatry. 2018;75(3):270–9. DOI: 10.1001/jamapsychiatry.2017.4327. PMID: 29387877; PMCID: PMC5885954
13. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry. 1987;44(7):660–9. DOI: 10.1001/archpsyc.1987.01800190080012. PMID: 3606332
14. Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? Br Med J (Clin Res Ed). 1987;295(6600):681–2. DOI: 10.1136/bmj.295.6600.681. PMID: 3117295; PMCID: PMC1247717
15. Owen MJ, O'Donovan MC. Schizophrenia and the neurodevelopmental continuum:evidence from genomics. World Psychiatry. 2017;16(3):227–35. DOI: 10.1002/wps.20440. PMID: 28941101; PMCID: PMC5608820
16. Trotta A, Murray RM, MacCabe JH. Do premorbid and post-onset cognitive functioning differ between schizophrenia and bipolar disorder? A systematic review and meta-analysis. Psychol Med. 2015;45(2):381–94. DOI: 10.1017/S0033291714001512. PMID: 25065268
17. Meier MH, Caspi A, Reichenberg A, Keefe RS, Fisher HL, Harrington H, et al. Neuropsychological decline in schizophrenia from the premorbid to the postonset period: evidence from a population-representative longitudinal study. Am J Psychiatry. 2014;171(1):91–101. DOI: 10.1176/appi.ajp.2013.12111438. PMID: 24030246; PMCID: PMC3947263
18. Jonas K, Lian W, Callahan J, Ruggero CJ, Clouston S, Reichenberg A, et al. The course of general cognitive ability in individuals with psychotic disorders. JAMA Psychiatry. 2022;79(7):659–66. DOI: 10.1001/jamapsychiatry.2022.1142. PMID: 35583896; PMCID: PMC9118026
19. Bora E, Murray RM. Meta-analysis of cognitive deficits in ultra-high risk to psychosis and first-episode psychosis: do the cognitive deficits progress over, or after, the onset of psychosis? Schizophr Bull. 2014;40(4):744–55. DOI: 10.1093/schbul/sbt085. PMID: 23770934; PMCID: PMC4059428
20. Watson AJ, Harrison L, Preti A, Wykes T, Cella M. Cognitive trajectories following onset of psychosis: a meta-analysis. Br J Psychiatry. 2022;221(6):714–21. DOI: 10.1192/bjp.2022.131. PMID: 36149012
21. Gebreegziabhere Y, Habatmu K, Mihretu A, Cella M, Alem A. Cognitive impairment in people with schizophrenia: an umbrella review. Eur Arch Psychiatry Clin Neurosci. 2022;272(7):1139–55. DOI: 10.1007/s00406-022-01416-6. PMID: 35633394; PMCID: PMC9508017
22. Cai L, Huang J. Schizophrenia and risk of dementia: a meta-analysis study. Neuropsychiatr Dis Treat. 2018;14:2047–55. DOI: 10.2147/NDT.S172933. PMID: 30147318; PMCID: PMC6095111
23. Stroup TS, Olfson M, Huang C, Wall MM, Goldberg T, Devanand DP, et al. Age-specific prevalence and incidence of dementia diagnoses among older US

adults with schizophrenia. JAMA Psychiatry. 2021;78(6):632–41. DOI: 10.1001/jamapsychiatry.2021.0042. PMID: 33688938; PMCID: PMC7948106
24. Stone WS, Phillips MR, Yang LH, Kegeles LS, Susser ES, Lieberman JA. Neurodegenerative model of schizophrenia: growing evidence to support a revisit. Schizophr Res. 2022;243:154–62. DOI: 10.1016/j.schres.2022.03.004. PMID: 35344853; PMCID: PMC9189010
25. Jonas K, Abi-Dargham A, Kotov R. Two hypotheses on the high incidence of dementia in psychotic disorders. JAMA Psychiatry. 2021;78(12):1305–6. DOI: 10.1001/jamapsychiatry.2021.2584. PMID: 34524413; PMCID: PMC10805107
26. Murray RM, Bora E, Modinos G, Vernon A. Schizophrenia: a developmental disorder with a risk of non-specific but avoidable decline. Schizophr Res. 2022;243:181–6. DOI: 10.1016/j.schres.2022.03.005. PMID: 35390609
27. Legge SE, Santoro ML, Periyasamy S, Okewole A, Arsalan A, Kowalec K. Genetic architecture of schizophrenia: a review of major advancements. Psychol Med. 2021;51(13):2168–77. DOI: 10.1017/S0033291720005334. PMID: 33550997
28. Trubetskoy V, Pardinas AF, Qi T, Panagiotaropoulou G, Awasthi S, Bigdeli TB, et al. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature. 2022;604(7906):502–8. DOI: 10.1038/s41586-022-04434-5. PMID: 35396580; PMCID: PMC9392466
29. Lee SH, DeCandia TR, Ripke S, Yang J; Schizophrenia Psychiatric Genome-Wide Association Study Consortium (PGC-SCZ); International Schizophrenia Consortium (ISC), et al. Estimating the proportion of variation in susceptibility to schizophrenia captured by common SNPs. Nat Genet. 2012;44(3):247–50. DOI: 10.1038/ng.1108. PMID: 22344220; PMCID: PMC3327879
30. Ripke S, O'Dushlaine C, Chambert K, Moran JL, Kahler AK, Akterin S, et al. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nat Genet. 2013;45(10):1150–9. DOI: 10.1038/ng.2742. PMID: 23974872; PMCID: PMC3827979
31. Rees E, Walters JT, Georgieva L, Isles AR, Chambert KD, Richards AL, et al. Analysis of copy number variations at 15 schizophrenia-associated loci. Br J Psychiatry. 2014;204(2):108–14. DOI: 10.1192/bjp.bp.113.131052. PMID: 24311552; PMCID: PMC3909838
32. Marshall CR, Howrigan DP, Merico D, Thiruvahindrapuram B, Wu W, Greer DS, et al. Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects. Nat Genet. 2017;49(1):27–35. DOI: 10.1038/ng.3725. PMID: 27869829; PMCID: PMC5737772
33. Fromer M, Pocklington AJ, Kavanagh DH, Williams HJ, Dwyer S, Gormley P, et al. De novo mutations in schizophrenia implicate synaptic networks. Nature. 2014;506(7487):179–84. DOI: 10.1038/nature12929. PMID: 24463507; PMCID: PMC4237002
34. Singh T, Kurki MI, Curtis D, Purcell SM, Crooks L, McRae J, et al. Rare loss-of-function variants in SETD1A are associated with schizophrenia and developmental disorders. Nat Neurosci. 2016;19(4):571–7. DOI: 10.1038/nn.4267. PMID: 26974950; PMCID: PMC6689268
35. Genovese G, Fromer M, Stahl EA, Ruderfer DM, Chambert K, Landen M, et al. Increased burden of ultra-rare protein-altering variants among 4,877 individuals with schizophrenia. Nat Neurosci. 2016;19(11):1433–41. DOI: 10.1038/nn.4402. PMID: 27694994; PMCID: PMC5104192
36. Howrigan DP, Rose SA, Samocha KE, Fromer M, Cerrato F, Chen WJ, et al. Exome sequencing in schizophrenia-affected parent-offspring trios reveals risk conferred by protein-coding de novo mutations. Nat Neurosci. 2020;23(2):185–93. DOI: 10.1038/s41593-019-0564-3. PMID: 31932770; PMCID: PMC7007385
37. Singh T, Walters JTR, Johnstone M, Curtis D, Suvisaari J, Torniainen M, et al. The contribution of rare variants to risk of schizophrenia in individuals with and without intellectual disability. Nat Genet. 2017;49(8):1167–73. DOI: 10.1038/ng.3903. PMID: 28650482; PMCID: PMC5533219
38. Singh T, Poterba T, Curtis D, Akil H, Al Eissa M, Barchas JD, et al. Rare coding variants in ten genes confer substantial risk for schizophrenia. Nature. 2022;604(7906):509–16. DOI: 10.1038/s41586-022-04556-w. PMID: 35396579; PMCID: PMC9805802
39. Rees E, Han J, Morgan J, Carrera N, Escott-Price V, Pocklington AJ, et al. De novo mutations identified by exome sequencing implicate rare missense variants in SLC6A1 in schizophrenia. Nat Neurosci. 2020;23(2):179–84. DOI: 10.1038/s41593-019-0565-2. PMID: 31932766; PMCID: PMC7007300
40. Liu D, Meyer D, Fennessy B, Feng C, Cheng E, Johnson JS, et al. Schizophrenia risk conferred by rare protein-truncating variants is conserved across diverse human populations. Nat Genet. 2023;55(3):369–76. DOI: 10.1038/s41588-023-01305-1. PMID: 36914870; PMCID: PMC10011128
41. O'Donovan MC, Owen MJ. The implications of the shared genetics of psychiatric disorders. Nat Med. 2016;22(11):1214–9. DOI: 10.1038/nm.4196. PMID: 27783064
42. Palmer DS, Howrigan DP, Chapman SB, Adolfsson R, Bass N, Blackwood D, et al. Exome sequencing in bipolar disorder identifies AKAP11 as a risk gene shared with schizophrenia. Nat Genet. 2022;54(5):541–7. DOI: 10.1038/s41588-022-01034-x. PMID: 35410376; PMCID: PMC9117467
43. Rees E, Kendall K, Pardinas AF, Legge SE, Pocklington A, Escott-Price V, et al. Analysis of intellectual disability copy number variants for association with schizophrenia. JAMA Psychiatry. 2016;73(9):963–9. DOI: 10.1001/jamapsychiatry.2016.1831. PMID: 27602560; PMCID: PMC5014093
44. Rees E, Creeth HDJ, Hwu HG, Chen WJ, Tsuang M, Glatt SJ, et al. Schizophrenia, autism spectrum disorders and developmental disorders share specific disruptive coding mutations. Nat Commun. 2021;12(1):5353. DOI: 10.1038/s41467-021-25532-4. PMID: 34504065; PMCID: PMC8429694
45. Bouchard TJ Jr., McGue M. Familial studies of intelligence: a review. Science. 1981;212(4498):1055–9. DOI: 10.1126/science.7195071. PMID: 7195071
46. Savage JE, Jansen PR, Stringer S, Watanabe K, Bryois J, de Leeuw CA, et al. Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. Nat Genet. 2018;50(7):912–9. DOI: 10.1038/s41588-018-0152-6. PMID: 29942086; PMCID: PMC6411041
47. Stefansson H, Meyer-Lindenberg A, Steinberg S, Magnusdottir B, Morgen K, Arnarsdottir S, et al. CNVs conferring risk of autism or schizophrenia affect cognition in controls. Nature. 2014;505(7483):361–6. DOI: 10.1038/nature12818. PMID: 24352232
48. Kendall KM, Rees E, Escott-Price V, Einon M, Thomas R, Hewitt J, et al. Cognitive performance among carriers of pathogenic copy number variants: analysis of 152,000 UK biobank subjects. Biol Psychiatry. 2017;82(2):103–10. DOI: 10.1016/j.biopsych.2016.08.014. PMID: 27773354
49. Gardner EJ, Neville MDC, Samocha KE, Barclay K, Kolk M, Niemi MEK, et al. Reduced reproductive success is associated with selective constraint on human genes. Nature. 2022;603(7903):858–63. DOI: 10.1038/s41586-022-04549-9. PMID: 35322230
50. Chen CY, Tian R, Ge T, Lam M, Sanchez-Andrade G, Singh T, et al. The impact of rare protein coding genetic variation on adult cognitive function. Nat Genet. 2023;55(6):927–38. DOI: 10.1038/s41588-023-01398-8. PMID: 37231097; PMCID: PMC10260403
51. Sitskoorn MM, Aleman A, Ebisch SJ, Appels MC, Kahn RS. Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. Schizophr Res. 2004;71(2-3):285–95. DOI: 10.1016/j.schres.2004.03.007. PMID: 15474899
52. Snitz BE, Macdonald AW 3rd, Carter CS. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. Schizophr Bull. 2006;32(1):179–94. DOI: 10.1093/schbul/sbi048. PMID: 16166612; PMCID: PMC2632195
53. Calkins ME, Ray A, Gur RC, Freedman R, Green MF, Greenwood TA, et al. Sex differences in familiality effects on neurocognitive performance in schizophrenia. Biol Psychiatry. 2013;73(10):976–84. DOI: 10.1016/j.biopsych.2012.12.021. PMID: 23395246; PMCID: PMC3954126
54. Kendler KS, Ohlsson H, Mezuk B, Sundquist JO, Sundquist K. Observed cognitive performance and deviation from familial cognitive aptitude at age 16 years and ages 18 to 20 years and risk for schizophrenia and bipolar illness in a swedish national sample. JAMA Psychiatry. 2016;73(5):465–71. DOI: 10.1001/jamapsychiatry.2016.0053. PMID: 27028264
55. Velthorst E, Mollon J, Murray RM, de Haan L, Germeys IM, Glahn DC, et al. Cognitive functioning throughout adulthood and illness stages in individuals with psychotic disorders and their unaffected siblings. Mol Psychiatry. 2021;26(8):4529–43. DOI: 10.1038/s41380-020-00969-z. PMID: 33414498
56. Greve AN, Uher R, Als TD, Jepsen JRM, Mortensen EL, Gantriis DL, et al. A nationwide cohort study of nonrandom mating in schizophrenia and bipolar disorder. Schizophr Bull. 2021;47(5):1342–50. DOI: 10.1093/schbul/sbab021. PMID: 33772315; PMCID: PMC8379547
57. Kendler KS, Ohlsson H, Sundquist J, Sundquist K. IQ and schizophrenia in a Swedish national sample: their causal relationship and the interaction of IQ with genetic risk. Am J Psychiatry. 2015;172(3):259–65. DOI: 10.1176/appi.ajp.2014.14040516. PMID: 25727538; PMCID: PMC4391822
58. Weckstrom T, Elovainio M, Pulkki-Raback L, Suokas K, Komulainen K, Mullola S, et al. School achievement in adolescence and the risk of mental disorders in early adulthood: a Finnish nationwide register study. Mol Psychiatry. 2023;28(7):3104–10. DOI: 10.1038/s41380-023-02081-4. PMID: 37131077; PMCID: PMC10615737
59. Demange PA, Boomsma DI, van Bergen E, Nivard MG. Evaluating the causal relationship between educational attainment and mental health. medRxiv. 2024. DOI: 10.1101/2023.01.26.23285029. PMID: 36747639; PMCID: PMC9901051
60. Kendler KS, Ohlsson H, Keefe RSE, Sundquist K, Sundquist J. The joint impact of cognitive performance in adolescence and familial cognitive aptitude on risk for major psychiatric disorders: a delineation of four potential pathways to illness. Mol Psychiatry. 2018;23(4):1076–83. DOI: 10.1038/mp.2017.78. PMID: 28416810; PMCID: PMC5647225
61. Hochberger WC, Combs T, Reilly JL, Bishop JR, Keefe RSE, Clementz BA, et al. Deviation from expected cognitive ability across psychotic disorders. Schizophr Res. 2018;192:300–7. DOI: 10.1016/j.schres.2017.05.019. PMID: 28545944; PMCID: PMC5699979

62. Mitchell BL, Hansell NK, McAloney K, Martin NG, Wright MJ, Renteria ME, et al. Polygenic influences associated with adolescent cognitive skills. Intelligence. 2022;94;101680. DOI: 10.1016/j.intell.2022.101680
63. Fowler T, Zammit S, Owen MJ, Rasmussen F. A population-based study of shared genetic variation between premorbid IQ and psychosis among male twin pairs and sibling pairs from Sweden. Arch Gen Psychiatry. 2012;69(5):460–6. DOI: 10.1001/archgenpsychiatry.2011.1370. PMID: 22566578
64. Border R, Athanasiadis G, Buil A, Schork AJ, Cai N, Young AI, et al. Cross-trait assortative mating is widespread and inflates genetic correlation estimates. Science. 2022;378(6621):754–61. DOI: 10.1126/science.abo2059. PMID: 36395242; PMCID: PMC9901291
65. Veller C, Coop GM. Interpreting population- and family-based genome-wide association studies in the presence of confounding. PLoS Biol. 2024; 22(4):e3002511. DOI: 10.1371/journal.pbio.3002511. PMID: 38603516; PMCID: PMC11008796
66. Toulopoulou T, Zhang X, Cherny S, Dickinson D, Berman KF, Straub RE, et al. Polygenic risk score increases schizophrenia liability through cognition-relevant pathways. Brain. 2019;142(2):471–85. DOI: 10.1093/brain/awy279. PMID: 30535067; PMCID: PMC6359897
67. Burton SMI, Sallis HM, Hatoum AS, Munafo MR, Reed ZE. Is there a causal relationship between executive function and liability to mental health and substance use? A Mendelian randomization approach. R Soc Open Sci. 2022;9(12):220631. DOI: 10.1098/rsos.220631. PMID: 36533203; PMCID: PMC9748493
68. Hindley G, Frei O, Shadrin AA, Cheng W, O'Connell KS, Icick R, et al. Charting the landscape of genetic overlap between mental disorders and related traits beyond genetic correlation. Am J Psychiatry. 2022;179(11):833–43. DOI: 10.1176/appi.ajp.21101051. PMID: 36069018; PMCID: PMC9633354
69. Legge SE, Cardno AG, Allardyce J, Dennison C, Hubbard L, Pardinas AF, et al. Associations between schizophrenia polygenic liability, symptom dimensions, and cognitive ability in schizophrenia. JAMA Psychiatry. 2021;78(10):1143–51. DOI: 10.1001/jamapsychiatry.2021.1961. PMID: 34347035; PMCID: PMC8340009
70. Richards AL, Pardinas AF, Frizzati A, Tansey KE, Lynham AJ, Holmans P, et al. The relationship between polygenic risk scores and cognition in schizophrenia. Schizophr Bull. 2020;46(2):336–44. DOI: 10.1093/schbul/sbz061. PMID: 31206164; PMCID: PMC7442352
71. Song J, Yao S, Kowalec K, Lu Y, Sariaslan A, Szatkiewicz JP, et al. The impact of educational attainment, intelligence and intellectual disability on schizophrenia: a Swedish population-based register and genetic study. Mol Psychiatry. 2022;27(5):2439–47. DOI: 10.1038/s41380-022-01500-2. PMID: 35379910; PMCID: PMC9135619
72. van Scheltinga AF, Bakker SC, van Haren NE, Derks EM, Buizer-Voskamp JE, Cahn W, et al. Schizophrenia genetic variants are not associated with intelligence. Psychol Med. 2013;43(12):2563–70. DOI: 10.1017/S0033291713000196. PMID: 23410598; PMCID: PMC4743754
73. Dickinson D, Zaidman SR, Giangrande EJ, Eisenberg DP, Gregory MD, Berman KF. Distinct polygenic score profiles in schizophrenia subgroups with different trajectories of cognitive development. Am J Psychiatry. 2020;177(4):298–307. DOI: 10.1176/appi.ajp.2019.19050527. PMID: 31838871; PMCID: PMC9627722
74. Shafee R, Nanda P, Padmanabhan JL, Tandon N, Alliey-Rodriguez N, Kalapurakkel S, et al. Polygenic risk for schizophrenia and measured domains of cognition in individuals with psychosis and controls. Transl Psychiatry. 2018;8(1):78. DOI: 10.1038/s41398-018-0124-8. PMID: 29643358; PMCID: PMC5895806
75. Jonas KG, Lencz T, Li K, Malhotra AK, Perlman G, Fochtmann LJ, et al. Schizophrenia polygenic risk score and 20-year course of illness in psychotic disorders. Transl Psychiatry. 2019;9(1):300. DOI: 10.1038/s41398-019-0612-5. PMID: 31727878; PMCID: PMC6856168
76. Creeth HDJ, Rees E, Legge SE, Dennison CA, Holmans P, Walters JTR, et al. Ultrarare coding variants and cognitive function in schizophrenia. JAMA Psychiatry. 2022;79(10):963–70. DOI: 10.1001/jamapsychiatry.2022.2289. PMID: 35976659; PMCID: PMC9386603
77. Hubbard L, Rees E, Morris DW, Lynham AJ, Richards AL, Pardinas AF, et al. Rare copy number variants are associated with poorer cognition in schizophrenia. Biol Psychiatry. 2021;90(1):28–34. DOI: 10.1016/j.biopsych.2020.11.025. PMID: 33678419
78. Rammos A, Kirov G, Hubbard L, Walters JTR, Holmans P, Owen MJ, et al. Family-based analysis of the contribution of rare and common genetic variants to school performance in schizophrenia. Mol Psychiatry. 2023;28:2081–7. DOI: 10.1038/s41380-023-02013-2. PMID: 36914811; PMCID: PMC10575776
79. Li C, Yang T, Ou R, Shang H. Overlapping genetic architecture between schizophrenia and neurodegenerative disorders. Front Cell Dev Biol. 2021;9:797072. DOI: 10.3389/fcell.2021.797072. PMID: 35004692; PMCID: PMC8740133
80. McLaughlin RL, Schijven D, van Rheenen W, van Eijk KR, O'Brien M, Kahn RS, et al. Genetic correlation between amyotrophic lateral sclerosis and schizophrenia. Nat Commun. 2017;8:14774. DOI: 10.1038/ncomms14774. PMID: 28322246; PMCID: PMC5364411
81. Brainstorm C, Anttila V, Bulik-Sullivan B, Finucane HK, Walters RK, Bras J, et al. Analysis of shared heritability in common disorders of the brain. Science. 2018;360(6395):eaap8757. DOI: 10.1126/science.aap8757. PMID: 29930110; PMCID: PMC6097237
82. Owen MJ, Legge SE, Rees E, Walters JTR, O'Donovan MC. Genomic findings in schizophrenia and their implications. Mol Psychiatry. 2023;28(9):3638–47. DOI: 10.1038/s41380-023-02293-8. PMID: 37853064; PMCID: PMC10730422
83. White TJH. Brain development and stochastic processes during prenatal and early life: you can't lose it if you've never had it; but it's better to have it and lose it, than never to have had it at all. J Am Acad Child Adolesc Psychiatry. 2019;58(11):1042–50. DOI: 10.1016/j.jaac.2019.02.010. PMID: 31327672
84. Berkson J. Limitations of the application of fourfold table analysis to hospital data. Biometrics. 1946;2(3):47–53. PMID: 21001024
85. Tansey KE, Rees E, Linden DE, Ripke S, Chambert KD, Moran JL, et al. Common alleles contribute to schizophrenia in CNV carriers. Mol Psychiatry. 2016;21(8):1085–9. DOI: 10.1038/mp.2015.143. PMID: 26390827; PMCID: PMC4960448
86. Cleynen I, Engchuan W, Hestand MS, Heung T, Holleman AM, Johnston HR, et al. Genetic contributors to risk of schizophrenia in the presence of a 22q11.2 deletion. Mol Psychiatry. 2021;26(8):4496–510. DOI: 10.1038/s41380-020-0654-3. PMID: 32015465; PMCID: PMC7396297
87. Craddock N, Owen MJ. The Kraepelinian dichotomy – going, going ... but still not gone. Br J Psychiatry. 2010;196(2):92–5. DOI: 10.1192/bjp.bp.109.073429. PMID: 20118450; PMCID: PMC2815936
88. Keefe RS, Reichenberg A. Predicting schizophrenia. JAMA Psychiatry. 2016;73(5):441–2. DOI: 10.1001/jamapsychiatry.2016.0138. PMID: 27028053
89. Cameron D, Mi D, Vinh NN, Webber C, Li M, Marin O, et al. Single-nuclei RNA sequencing of 5 regions of the human prenatal brain implicates developing neuron populations in genetic risk for schizophrenia. Biol Psychiatry. 2023;93(2):157–66. DOI: 10.1016/j.biopsych.2022.06.033. PMID: 36150908; PMCID: PMC10804933
90. Crawford JR, Deary IJ, Starr J, Whalley LJ. The NART as an index of prior intellectual functioning: a retrospective validity study covering a 66-year interval. Psychol Med. 2001;31(3):451–8. DOI: 10.1017/s0033291701003634. PMID: 11305853