



# The genetics of cognition in schizophrenia

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**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.**

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## 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

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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 rela-

tives 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 re-

fect 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).

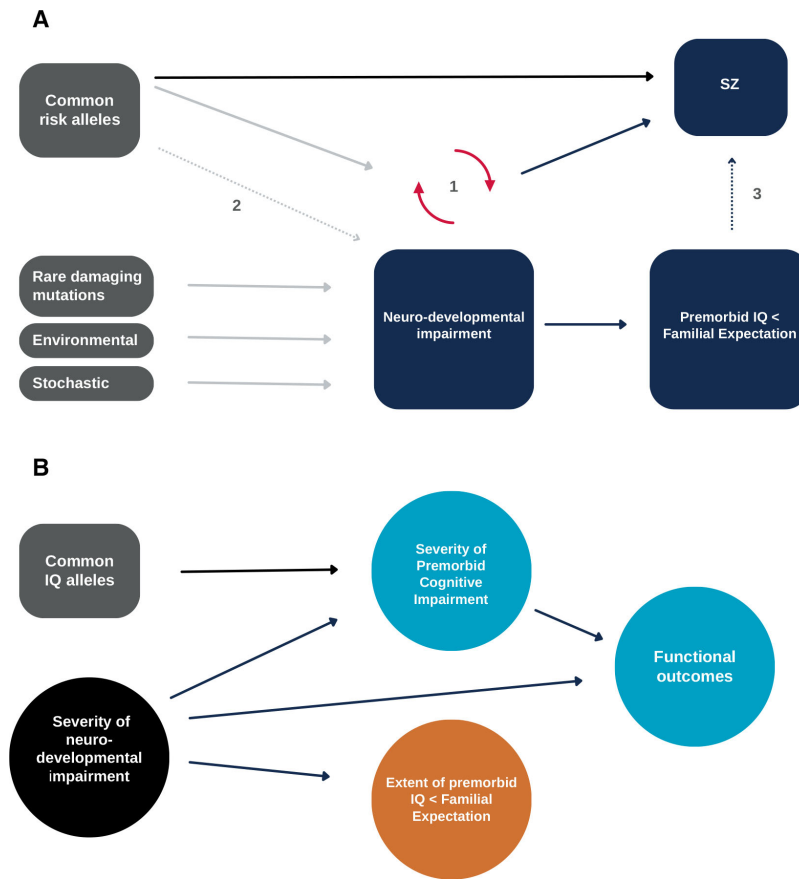
We additionally note that while our focus here is schizophrenia, comparisons of the degree of premorbid deviation from familial cognitive aptitude (60) in different psychiatric disorders support the view that the neurodevelopmental continuum extends across a number of conditions, as previously proposed (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.

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## Author Contributions

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