On the Origins of Schizophrenia

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What have we accomplished for schizophrenia patients since the introduction of chlorpromazine in 1952 (1)? Have we really made a difference in the outcome of schizophrenia? When we examine objective and clinically meaningful "hard" outcomes, the answer appears to be negative. Still only about 10% of schizophrenia patients will find (or hold) gainful employment (2). Life expectancy in schizophrenia is reduced by almost 15 years, and this has not improved over recent decades (3). Patients with schizophrenia are rarely able to establish a family, at least when judged by reproductive fitness or fecundity (4). The reason is not that antipsychotics are ineffective; in fact, they are highly successful in what they were designed to accomplish, which is to reduce psychosis (at least during the initial phase of the illness). Almost two-thirds of first-episode schizophrenia patients reach remission after 4 to 10 weeks of antipsychotic treatment (5); even after 1 year of treatment, two-thirds are doing well (6).

So why have these medications not been able to significantly improve the long-term prognosis of schizophrenia patients? One of the reasons is that patients fail to continue treatment. Indeed, when antipsychotics are used uninterruptedly, mortality is reduced (7) and outcome, expressed as rehospitalization, improves (8). However, I propose that the principal reason that we have not been able to materially ameliorate the outcome in schizophrenia is that we have been barking up the wrong tree; we have mistakenly focused on psychosis.

Neither Kraepelin nor Bleuler considered psychosis as the core symptom of what we now call schizophrenia; neither defined schizophrenia on the basis of it. Kraepelin delineated the illness on the cognitive decline preceding the onset of psychosis—which he therefore named dementia praecox. Indeed, when Kraepelin first described the disorder, in the 4th edition of his textbook (which has never been translated into English), he starts the narrative with the slow but steady cognitive decline during adolescence (9). His account of the cognitive (and social) decline precedes the first mention of psychotic symptoms by six pages, indicating the relative priority—both in chronology and in relevance—he attributed to cognition rather than psychosis. Bleuler (10) viewed delusions and hallucinations as accessory symptoms as well; the basis of the illness was, according to him, determined by disturbance in affect, cognition (associative thinking), social interaction (autism), and volition (ambivalence). So why has research—and drug development—focused so much on that one symptom, or syndrome, in schizophrenia, even to the extent that schizophrenia and psychosis are seen as one and the same? Could the reason be just *because* our medications are so effective in treating this aspect of schizophrenia? Indeed, it is the treatability of psychosis and, conversely, the stigma associated with the poor outcome of schizophrenia, that is—mistakenly (11)—used as an argument to question the validity of the schizophrenia concept (12). Focusing on psychosis instead of on the defining phenotype of schizophrenia may well be the reason the field has made little material progress in improving its outcome.

COGNITIVE DECLINE IN ADOLESCENCE: RENEWED FOCUS ON A CENTURY-OLD OBSERVATION

The emphasis on psychosis has permeated our textbooks; consequently our students are still taught that schizophrenia debuts in early adulthood—because that is indeed when the first signs of psychosis usually present themselves to the health care provider. However, several well-designed retrospective and prospective studies show that the first signs of the illness precede the onset of psychosis by a decade or more. Entirely consistent with Kraepelin's original observations, abundant evidence has accumulated that schizophrenia does not debut with psychosis but with much more subtle deviations from the norm, expressed in motor, social, and cognitive behavior (13, 14). The data on cognition are most compelling. Linking cognitive testing results from the Israeli draft board with those of the National Psychiatric Hospitalization Case Registry, Reichenberg et al. (15) found significant premorbid deficits on intellectual measures during the draft assessment (at ages 16–17) in those who later developed schizophrenia. This was confirmed, using school achievement as an indication of intellectual performance, in a population-wide study relating data from the Swedish National School Register (also acquired at age 16) to the Swedish Hospital Discharge Register (16). Among psychiatric disorders, lower IQ as a premorbid marker of illness appears to be specific to this disorder; a recent review concluded that individuals who later develop schizophrenia, but not those who

develop related psychotic illnesses such as bipolar disorder, exhibit an IQ deficit prior to presentation of the first psychosis (17). It was estimated, again using data from the Israeli draft board, that poor school performance precedes the onset of the illness by almost a decade (18). This is consistent with results from our study comparing scholastic aptitude in twins discordant for schizophrenia, where the twin who would go on to develop schizophrenia showed poorer school performance more than a decade before psychosis onset (19).

Prospective studies assessing participants from birth—and therefore able to identify changes much earlier than the aforementioned retrospective studies—found the first signs of schizophrenia to occur during the early teens, if not earlier. Specifically, studies of birth cohorts from New Zealand and the United Kingdom find poorer cognitive performance at age 13 (20, 21) and possibly even at age 4 or age 8 (21) in those who are later diagnosed with schizophrenia. Also, cognitive function is lower than would be expected on the basis of the educational attainment of their first-degree relatives (22), suggesting that this underperformance is related to the risk of developing the illness. Thus, there is little doubt that cognitive function starts to decline many years before the first psychotic symptoms manifest themselves in the context of schizophrenia. Equally relevant, this phenomenon is related to the development of schizophrenia and not to psychosis per se.

LOWER COGNITIVE FUNCTION PRECEDING THE ONSET OF PSYCHOSIS

The realization that schizophrenia debuts well before patients present with psychosis or are hospitalized has led to the concept of studying individuals who have some psychotic symptoms but do not (yet) fulfill the full criteria for psychosis, let alone schizophrenia. The concept goes by various names and acronyms, such as at-risk mental state (ARMS), ultra high risk (UHR), and, when help seeking, clinical high risk (CHR) (23). All have in common that the patients are defined by so-called attenuated psychotic symptoms with the outcome defined as "conversion" or "transition" to full psychosis—not necessarily schizophrenia. One of the more problematic, although interesting, issues with the CHR concept is that even in this subsyndromal population, transition to full psychosis is rare: about 15% (e.g., reference 24). Moreover, the concept of transition itself is criticized on the basis of the selective sampling of these cohorts and the fact that transition is a binary outcome defined as a higher score on the continuous scale that selected the population in the first place (25)—although recently suggestions have been made for improving sampling strategies (26). Nevertheless, the exclusive focus on psychosis (both at baseline and as outcome) in the CHR concept may be inherently flawed (25). Also, it is important to realize that the age range of the subjects included in these studies is usually very wide (from 12 to 35 years), with the upper end far too old to be credibly related to the development of schizophrenia. Nevertheless, the CHR studies have the potential to provide, if indirectly, interesting clues on the risk factors of schizophrenia: in the largest single study to date, including almost 700 CHR patients, cognitive impairment was present in the entire sample but was most pronounced in those who developed full psychosis—although here, as in most CHR studies, schizophrenia as an outcome was not reported (27). Studies examining the longitudinal course of cognitive development in CHR—essential to reliably draw conclusions on cognitive development in those cohorts—have not been published to date.

ABNORMAL BRAIN MATURATION PRECEDING THE ONSET OF PSYCHOSIS

The finding that cognitive decline in schizophrenia starts at, if not before, adolescence is consistent with studies examining brain structure in schizophrenia. More than four decades ago, Johnstone et al. (28) published their seminal paper reporting for the first time reduced brain volume (or, more precisely, increased lateral ventricle volume) in schizophrenia patients on the basis of CT scans. Since this concerned a cross-sectional study in chronic patients, the question remained as to *when* these changes manifest themselves. Since then, multiple studies in medication-naive patients with first-episode schizophrenia have shown that brain volumes are smaller at the first presentation of psychosis than those of matched control subjects (29). Consistently, CHR subjects who go on to develop a full psychotic episode exhibit smaller brain volumes before they receive antipsychotic medication (24). The fact that brain volumes are smaller in schizophrenia before the emergence of the first psychosis suggests that, contrary to what is sometimes suggested (30), the brain loss cannot be attributed to antipsychotic medication. Although the results from MRI studies in first-episode schizophrenia and CHR subjects suggest that brain loss is present at or before the first psychosis, they do not clarify at what time point the decreases in brain volume first become apparent. However, there is compelling evidence that the process leading to decreased brain volume starts well before the onset of psychosis. This conclusion is based on a simple but often overlooked variable: intracranial volume (ICV), or more simply put, skull size. ICV is a highly reliable measure that is often not assessed, or goes unreported, in neuroimaging studies in schizophrenia. Nevertheless, it is relevant because ICV directly reflects brain growth, as cranial growth is driven by the expansion of the brain. Although the exact age when the brain reaches it maximum size is somewhat variable, it is generally considered to be at the start of puberty (31). Thus, an ICV that is smaller in schizophrenia patients than in matched healthy control subjects must be due to stunted brain growth (at any point in time) before that age. Since the effect size is small and therefore often, if reported, is not significant in single studies, the results of our meta-analysis in over 18,000 subjects show a small ($d=0.2$) but highly significant reduction in ICV (29). These results indicate that some of the brain loss in schizophrenia is developmental in nature and

must occur before the early teens—that is, long before there is any indication of psychosis, let alone schizophrenia.

A relatively novel way to study brain development is the so-called brain-age gap—the difference between the "age" of the brain and the chronological age of a person. For instance, a 20-year-old may have a brain that resembles that of a 25-year-old person, in which case the brain-age gap is 5 years. We reported, examining brain age in a longitudinal study across a 50-year age span (16–67 years), that brain age was significantly higher (by 3.6 years) than chronological age in schizophrenia patients (32). Similarly, when the brain-age gap was studied in a CHR population, albeit in a cross-sectional study, it was found to significantly deviate from the norm in those who transitioned to psychosis (33). Thus, it appears from the available evidence, which admittedly is still scarce, that abnormal brain maturation starting before the mid-teens is related to the development of schizophrenia. However, large longitudinal studies focusing on young adolescents and using schizophrenia (in contrast to psychosis) as outcome are sorely needed.

COGNITIVE AND BRAIN ABNORMALITIES AND THE GENETIC RISK FOR SCHIZOPHRENIA

Cognitive function is related to brain structure in the healthy population: intelligence positively correlates with global brain volume, explaining a little over 6% of the variance (34). However, brain volume is not static, nor is IQ. Indeed, in a longitudinal study in 504 healthy subjects, we reported that intelligence is more related to the magnitude and timing of changes in brain structure than to brain structure per se (35), especially in early adolescence (36).

In medication-naive first-episode schizophrenia patients, lower IQ was related to smaller brain volumes (37), with most of the brain volume loss over time confined to the group of patients showing cognitive decline over the first years of illness (38). Thus, there is growing evidence that changes in IQ are related to (maturational) changes in the cortex, both in healthy subjects and in patients with schizophrenia. Intriguingly, this relationship seems itself age dependent and to present itself predominantly at the onset of puberty. What is more, it appears that genes that increase the risk of developing schizophrenia may drive the changes in both the brain and in cognition.

That schizophrenia is heritable has been suspected since the first days the illness was conceptualized; indeed, it was recently estimated that genetic variation contributes up to 85% of the risk of developing the illness (39). Brain volume and intelligence are highly heritable as well, with estimates up to 90% for total brain volume (40) and 80% for IQ (41). Thus, one may assume that if there is a genetic relationship between risk for schizophrenia and cognition, this risk may also be expressed in brain volume loss. Indeed, on the basis of 1,243 twins, using mathematical models, we concluded that 25% of the total risk variance for schizophrenia is explained by lower IQ, and 4% of this variance is explained by smaller brain volume (42). Taken together with the early onset of cognitive changes and the smaller intracranial volume found in schizophrenia, these results suggest that part of the genetic risk of developing the illness may be related to an abnormal early development of the brain leading to cognitive deficits. The brain changes appear to be primarily expressed in cortical thickness and white matter integrity (43). However, it is more likely that the substrate in the brain underlying the cognitive changes in the development of schizophrenia is related to abnormal connectivity rather than gross volume decreases.

BRAIN NETWORKS AND COGNITIVE CHANGES IN SCHIZOPHRENIA

Schizophrenia has been conceptualized as a disorder of brain connectivity since the illness was first defined (9, 10, 44), and this idea was revived a century later using more modern techniques (45). Consistent with these hypotheses, we have shown that white matter connectivity is disrupted in schizophrenia, particularly in those areas that form the hubs for the main connections in the brain (46, 47). In view of their rich interconnectedness, these hubs are sometimes collectively called the "rich club" (46). These networks, also called the "connectome" of the brain (48), are under genetic control (43, 49) and are already being formed in the second trimester of pregnancy (50). The efficiency of this network—defined as the optimal relationship between functional connectivity and distance between brain areas (51)—is highly related to intelligence (52), as are the observed changes in this network's efficiency during adolescence (49). Not only are brain networks under considerable genetic control, and not only are the abnormalities related to some of the genes conferring increased risk for schizophrenia, but also important changes in these networks crucially occur during early adolescence. In general, the cortex becomes thinner during adolescence (e.g., 53), with its connecting white matter fibers increasing in volume (54). The cortical changes are genetically controlled and are related to cognitive development during adolescence (55). Crucially, the brain networks become increasingly more efficiently organized during this period (49), with their efficiency increasing in adolescence between ages 10 and 13 (56) and the effect leveling off between ages 13 and 18. The connectome's efficiency itself and the relationship between intelligence and network efficiency are under genetic control (47% and 87%, respectively) (54). Thus, abnormal development of the brain's network appears to be a plausible candidate for the neuroanatomical and functional substrate of the cognitive changes that precede the onset of psychosis in schizophrenia. Moreover, in view of the high heritability, abnormalities in the networks' efficiency could possibly be related to the genetic risk of schizophrenia. Indeed, abnormal network efficiency in the rich club has been found in siblings (57) and offspring of schizophrenia patients (58). Interestingly, this effect in the rich club hubs appears to be specific for schizophrenia—it has not been found in patients with bipolar

disorder (59) or their offspring (58). Since the abnormalities are also observed in medication-naive schizophrenia patients, they cannot be attributed to the use of medication and are most likely present before illness onset (60). Moreover, connectome organization has been found to be related to functional outcome and decreases in IQ over time in schizophrenia patients (61). Importantly, the macroscopic hub areas of the brain, as identified with MRI, can also be determined on a cellular, microscopic level, and they are highly related to higher-order cognitive functions, such as IQ (62, 63). Moreover, when combining transcriptional profiles of schizophrenia risk genes with data on the decreased hub connectivity, we found that the expression profile of risk genes across cortical regions was significantly correlated with the regional dysconnectivity (64). In addition, effects were found to be potentially specific to schizophrenia, with transcriptional profiles not related to cortical dysconnectivity in patients with bipolar illness. Especially fascinating is the finding that brain connections present in humans but not in chimpanzees—those predominantly involved in semantic comprehension and language processing—are those affected in schizophrenia and not in other psychiatric disorders, such as autism, obsessive-compulsive disorder, and major depression (65), suggesting that the same areas that have evolved in humans to acquire higher-order cognitive capabilities, such as language, are those that are particularly vulnerable to being affected in the development of schizophrenia. Another line of evidence suggesting that brain development during adolescence is a crucial factor in the path to schizophrenia is derived from genetic studies.

BRAIN NETWORKS AND THE GENETICS OF SCHIZOPHRENIA

Currently more than 200 genome-wide significant loci have been associated with the risk of schizophrenia in Caucasian populations (66). The strongest genetic relationship is that across the major histocompatibility complex (MHC) locus on chromosome 6, which is known for its role in immunity. Sekar et al. (67) identified alleles of the complement component 4 (C4 genes) in the MHC region as underlying the MHC signal. Also, allelic variation in C4 was related to increased risk for schizophrenia in proportion to its promotion of expression of C4A mRNA. Sekar et al. also found increased levels of C4 mRNA expression in postmortem brain from individuals with schizophrenia compared with matched control subjects. This discovery was recently replicated in a transcriptomic study by the PsychEncode consortium that included 559 schizophrenia case subjects and 936 healthy control subjects (68). Relevant for the development of schizophrenia during adolescence, Stevens et al. (69) have shown that proteins of the complement system are involved in activity-dependent synaptic pruning: weak synapses are tagged by these complement proteins and eliminated by microglia. Similar properties were recently found for C4 (67). In a human in vitro model with induced neurons and microglia, Sellgren et al. (70) showed that microglia generated from stem cells of schizophrenia patients eliminated more synaptic structures, with both neuronal and microglial factors contributing. These studies have revitalized the hypothesis that schizophrenia may result from abnormalities in brain maturation (71), specifically abnormalities in the synaptic pruning of prefrontal and temporal cerebral cortex that normally characterizes adolescent brain maturation (72). Indeed, excessive loss of gray matter and abnormally low numbers of synapses on cortical neurons in these brain regions (i.e., excessive synaptic pruning) are well-replicated pathological findings in schizophrenia (73). The hypothesis on the role of increased complement activity as a pathogenic mechanism in schizophrenia elegantly links genetic, neuroanatomical, and phenotypical findings (74). Although it still needs to be properly tested, it provides an inspiring example of how data from various sources can help elucidate the causes of schizophrenia.

TRANSLATING OLD FINDINGS TO NEW INITIATIVES

In order to understand schizophrenia, its causes, development, and outcome, and in order to define new subgroups of patients who may be differentially responsive to treatment or, hopefully, prevention interventions, we will need to switch our focus from psychosis to cognition and the related brain development during childhood and early adolescence. It is clear that cognitive decline before the onset of psychosis is an important marker, if not a harbinger, of impending schizophrenia with the possibility, if identified appropriately early, that interventions can be developed to halt this decline and prevent psychosis (75). Thus, research efforts that target the second decade of life are essential if we are to find mechanisms for intervention and cure. These studies are costly and time-consuming, but there is an example that is rapidly providing some of this information: the UK Biobank, a unique initiative, is an open source of data that is producing the information that will help resolve the issues described above. For instance, in a study using UK Biobank data from more than 2,800 participants from the general population, a relationship was found between the polygenic risk score for schizophrenia and cortical thinning on MRI (76). These findings confirm—in the general population—the reported association between genetic vulnerability to the disorder and brain pathology in those at increased genetic risk for schizophrenia (77). Equally important, and showing the need for such large samples, individuals with rare copy number variants (CNVs) were identified in a study of over 400,000 subjects in the UK Biobank reporting a relationship between CNVs that are associated with an increased risk for schizophrenia and lower cognitive performance on neuropsychological tests (78). Finally, researchers using UK Biobank data were able to identify new loci related to cognitive function (79) and the related variable of educational attainment (80) in the general population—information that will be, for reasons outlined here, potentially relevant for the study of schizophrenia.

A comparable program in the United States is the Million Veteran Program (MVP), which is expected to be as informative and successful as the UK Biobank; indeed, recently Harvey et al. (81), using data from the MVP, reported robust associations between greater polygenic loading for schizophrenia risk and poorer cognitive performance.

Clearly, more of such large-scale initiatives will be needed, and they need to longitudinal. Although some cohorts are being followed—the Adolescent Brain and Cognitive Development study comes to mind (82)—their numbers will still be too low to detect causes for relatively rare disorders such as schizophrenia (of the 10,000 subjects included, only 100 are expected to develop schizophrenia).

In addition to these large population-based studies, subjects can be followed who are at greatly increased risk for schizophrenia, which requires, given the large relative risk ratios, much smaller numbers. Schizophrenia risk is probably increased through a combination of many common variants, more of which are being identified as sample sizes are increasing (83). However, the explained risk is very low for each of these variants, and even these variants in combination. Much larger effects are seen in the people who carry very rare CNVs. Although results obtained from following these subjects will be difficult to interpret in view of their scarcity in the population and less generalizable than results from samples from the general population, they are helpful in studying mechanistic questions. One promising example is the identification of *SETD1A* as a schizophrenia susceptibility gene (84). Loss of function in this gene was recently shown to negatively affect the brain connectome in mice, which in turn was related to cognitive deficits in these animals (85).

The usefulness of examining the role of rare variants has also proven its merit in human studies, such as adolescents with the 22q11.2 deletion syndrome (22q11DS), who have a 25-fold increased risk of developing schizophrenia (86). When cognitive function was assessed longitudinally in a group of 829 children and adolescents with this syndrome, cognitive performance declined in the entire group of patients, but it was most pronounced in those who went on to develop schizophrenia (87). Since the 22q11DS is rare—1:4,000 for deletions and 1:1,600 for duplications in the 22q11.2 area (88)—this study could only be successful because all researchers working in this field shared their data. Finally, studying another high-risk group, the offspring of patients with schizophrenia, is a good possibility for enriching samples for the development of schizophrenia. Indeed, long-term follow-up of offspring of patients with bipolar disorder has provided important information on the highly heterogeneous pathways to bipolar illness (89). Following offspring of schizophrenia patients, although more difficult given the decreased fecundity of schizophrenia patients (4), would be expected to be as informative.

CONCLUSIONS

Despite an enormous expansion in our knowledge on the etiology, pathophysiology, and illness course of schizophrenia, so far we have not been able to materially improve the outcome of this highly incapacitating illness. One of the reasons may be that we have been focusing on psychosis, which is a relatively late-occurring, and nonspecific, symptom of schizophrenia. It has become abundantly clear that schizophrenia debuts with cognitive decline years before the onset of the first psychosis. Cognitive and brain development are highly linked, especially during early adolescence, and both are, independently as well as their interaction, under substantial genetic control. A growing body of evidence suggests that abnormal brain maturation during the early teen years, especially that of the hub areas in the brain, may be causally related to the development of the disorder. These changes can be linked to specific genetic loci that have been found to increase the risk for schizophrenia and can be attributed to abnormal synaptic pruning during this developmental period. Large collaborative longitudinal (population based and high-risk) studies focusing on early adolescence and linking cognition, phenomenology, brain imaging, biomarkers, and genetics may be the path forward to elucidate the causes of schizophrenia. We should then be able to develop the tools to finally improve outcomes for the patients suffering from this devastating disorder.

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