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Why Kraepelin Was Right

Schizophrenia as a Cognitive Disorder

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Abstract

Classification of schizophrenia as a psychotic disorder has greatly inhibited progress in understanding and treating the disorder, as cognitive underperformance lies at the core of schizophrenia. Cognitive function is an important determinant of global functional outcome. This chapter reviews evidence in support of the view that schizophrenia is a cognitive disorder. Risk factors, cognitive decline, and developmental trajectories are discussed, and the consequences of considering schizophrenia a cognitive instead of a psychotic disorder are explored. It is proposed that development of effective treatments needs to focus on the cognitive aspects of the disorder.

Introduction

Schizophrenia is currently classified as a psychotic disorder; be it DSM or ICD, schizophrenia is defined by its psychotic symptoms. This chapter will attempt to show that this emphasis on psychosis is not only a fallacy, it is an error that has greatly contributed to the lack of progress in our understanding of this illness and hence has hampered the development of adequate treatments. Indeed, prognosis of schizophrenia may not have changed substantially since the introduction of chlorpromazine over fifty years ago, and some argue it has not meaningfully improved since the illness was first described (Hegarty et al. 1994). One of the reasons may be that the focus on psychosis has obscured the obvious: schizophrenia is not a psychotic disorder; it is a cognitive illness.

Obviously, this notion is not new. When Kraepelin first delineated the disorder in 1893 he named it "dementia praecox" for a good reason: he considered the illness to be a cognitive one. Indeed, when Kraepelin first described the disorder in the fifth edition of his *Lehrbuch*, his description begins with the observation of slow (occasionally rapid) cognitive decline that he typically found in his patients during adolescence (Kraepelin 1896). In his opinion, the hallmark of the disorder is a decrease in intellectual performance that begins almost a decade before the onset of psychosis and continues for many years

thereafter. In fact, only after elaborating on this aspect of the illness for seven pages does he mention the presence of psychotic symptoms.[1] Kraepelin, of course, was not the only preeminent psychiatrist who considered psychosis to be a secondary or associated part of the illness. Bleuler (1911/1950), who coined the term "schizophrenia," viewed delusions and hallucinations as accessory symptoms as well; the core of this illness was determined by disturbance in affect, cognition (associative thinking), social interaction (autism), and volition (ambivalence).

Our current state of knowledge supports Kraepelin's notion of schizophrenia as a cognitive disorder for several reasons. First, low intelligence is a risk factor for schizophrenia. Second, cognitive decline and intellectual underperformance precede the onset of psychosis by many years. Third, decline in cognitive functioning continues after psychosis onset. Fourth, although cognitive underperformance prior to psychosis has not definitively been shown to be specific to schizophrenia, it does distinguish it from the "other" major psychotic illness (bipolar disorder). Finally, cognitive underperformance is an important predictor of general functional outcome in schizophrenia.

Low IQ as a (Genetically Mediated) Risk Factor

Low intelligence and intellectual underperformance have consistently been shown to constitute risk factors for the development of schizophrenia. A recent meta-analysis of 12 studies in population-based cohorts and nested case control studies, which included over 4,000 cases and more than 700,000 controls, found that low IQ increases the risk for developing schizophrenia in a dose-response fashion (with an effect size of 0.43): every point of decrease in IQ raised risk by 3.7% (Khandaker et al. 2011). A separate meta-analysis conducted by Dickson et al. (2012), which partially overlapped with the study by Khandaker et al. (2011), included only those studies which assessed participants aged 16 years or younger; Dickson et al. also found that low IQ increased the risk for schizophrenia, with an effect size of about 0.5. Interestingly, in this meta-analysis, risk was already evident by age 13, that is, many years prior to the onset of psychosis.

A different, but relevant indicator of intellectual underperformance—scholastic achievement—is also related to an increased risk of developing schizophrenia. In a nationwide cohort of Swedish individuals, school performance at age 16 was inversely related to the risk of developing schizophrenia in a dose-response fashion. Children who received the lowest grades had a fourfold risk

[1] In subsequent printings of the *Lehrbuch*, Kraepelin greatly expands on the description of this syndrome, eventually separating it into hebephrenic, katatonic, and paranoid subtypes. Even though psychotic features (e.g., hallucinations and delusions) gain prominence in the paranoid and katatonic subtypes, the hallmark of the disorder remains the cognitive decline during adolescence.

of developing the illness. Interestingly, repeating a school year (which occurs in some European countries when grades are insufficient) carried the highest risk: a hazard ratio of 9 (MacCabe et al. 2008).

Some of this risk may be, at least in part, related to the genetic risk of developing schizophrenia. Population-based studies in first-degree family members, as well as data obtained from selected samples and twin studies, all suggest that low IQ is related to the genetic risk of developing the illness (Aukes et al. 2009). In fact, it has been suggested that a substantial portion of the phenotypic correlation between schizophrenia and cognition is caused by shared genetic effects (Toulopoulou et al. 2010).

Cognitive Decline Prior to Onset of Psychosis

Although low IQ is a robust risk factor for schizophrenia, it is unclear whether low IQ is present at birth or is the result of a relative developmental *decline* in IQ that occurs at some point in time prior to the onset of psychosis (or both). Unfortunately, only a few studies have addressed this cardinal issue. One study compared childhood scholastic test performance in Iowa (the Iowa State tests of basic skills and educational development was used) from 70 subjects who later went on to develop schizophrenia with the population average. This scholastic test is administered to all children across the state of Iowa in grades 4, 8, and 11 (corresponding to the ages 9, 13, and 16) to assess five cognitive domains. Although the (prospective) patients did not differ from the State average at ages 9 and 13, they underperformed significantly at age 16 (with an effect size of around .35); this underperformance was most pronounced on language skills (Fuller et al. 2002). These results suggest that intellectual performance declines between the ages of 13 and 16 in individuals who go on to develop schizophrenia.

Retrospectively, we compared a robust and objective measure of high school performance (defined as "doubling" or repeating a grade, a mandatory measure in the Dutch schooling system when grades fall below a certain standard) in a sample of over 80 twins (MZ and DZ) discordant for schizophrenia with that of a matched sample of healthy twins. Not only did the twin who went on to develop schizophrenia underperform his or her unaffected co-twin in 90% of cases, this underperformance was evident at age 13 and preceded the onset of the first psychosis by an average of nine years (Van Oel et al. 2002). In a fully prospective study, Reichenberg et al. (2010) used data from the Dunedin birth cohort, where cognitive performance was tested at ages 7, 9, 11, and 13; final symptomatic follow-up was then conducted at age 32. Not only did the 35 subjects who went on to develop schizophrenia underperform their healthy cohort controls at all measurement points, they started to lag further behind their peers between the ages of 7 to 13 (Reichenberg et al. 2010). In short, these studies not only suggest that children who will go on to develop schizophrenia

progressively underperform their healthy peers, but that this (relative) decline in intellectual performance starts early in adolescence, years prior to the onset of psychosis.

Cognitive Function after Onset of Psychosis

Numerous studies have assessed global (or specific aspects of) intellectual functioning in schizophrenia once diagnosis is established, finding IQ to be about 2 standard deviations (SD) lower than age-matched controls (e.g., Keefe and Fenton 2007). Interestingly, only about 20% of the schizophrenia population can be considered to have an unimpaired IQ, defined as being less than 1 SD below the normal mean (Keefe and Fenton 2007). However, even this group may have a lower IQ than would be expected on the basis of the level of education in their respective families. Indeed, as Keefe et al. (2005) show, IQ in schizophrenia patients is lower than would be expected on the basis of the level of their mothers' education. This suggests that IQ may well be lower in all patients, certainly when compared to their (genetic and environmental) intellectual potential. However, the decrease in IQ does not indicate *when* the decline begins. As indicated, some of it occurs prior to the onset of psychosis, but does this decrease in IQ continue once psychosis is established? Since the degree of cognitive impairment of 2 SD in patients is (much) larger than the 0.5 SD observed in individuals prior to psychosis onset (Woodberry et al. 2008), it is highly likely that IQ continues to decline after psychosis sets in.

Although a considerable number of studies have examined intellectual functioning in patients with established schizophrenia over time, many are impossible to interpret. This is because most studies that have assessed IQ over time failed to include a healthy control group, so that effects of practice cannot be ruled out (Goldberg et al. 2007, 2010). In fact, very few studies have included healthy controls in their assessment of IQ change in schizophrenia over time. In a recent meta-analysis (Hedman et al. 2013), which summarizes data from eight studies (including 280 patients and 306 healthy controls), we conclude that IQ increases significantly less in patients over time (0.33 points) than it does in healthy controls (2.1 points), resulting in an effect size for (relative) cognitive decline of .48. Thus, although the number of studies and subjects attests to the lack of well-designed studies that examine cognitive change in schizophrenia, available results suggest that intellectual performance continues to decline after the onset of psychosis in schizophrenia.

Specificity of Cognitive Decline

Although the specificity of cognitive decline in schizophrenia has hardly been studied, it appears that cognitive dysfunction—at the very least prior to the

onset of psychosis—distinguishes it from the other major psychotic illness (i.e., according to current classification systems): bipolar disorder. Although the number of studies that examine cognition prior to the onset of bipolar disorder is more limited than those in schizophrenia, a consistent pattern has emerged: low IQ constitutes a risk factor for schizophrenia, but it does not in bipolar illness. Using data from the Israeli Draft Board, where IQ was assessed in adolescents, those who were later hospitalized for bipolar disorder did not differ in intellectual performance from the normal population (Reichenberg et al. 2002). Similarly, data from Swedish (Zammit et al. 2004) and Danish (Sørensen et al. 2012) draft boards suggest that draftees who later go on to be hospitalized for bipolar disorder do not differ significantly in IQ from healthy individuals. In fact, a recent study in over one million Swedish men found that high intelligence carried a 60% increased risk (HR 1.59) for later hospitalization for bipolar disorder, at least in those without comorbidity (Gale et al. 2013). Consistently, in a study examining school grades from all Swedish schoolchildren between 1988 and 1997, individuals with excellent school performance had an almost four times higher risk of developing bipolar illness compared to those with average grades (MacCabe et al. 2010). Clearly, low IQ is not a risk factor for bipolar illness.

The issue of whether a *decline* in cognitive function precedes the onset of bipolar disorder has not been addressed in population-based studies. However, we conducted a study in MZ and DZ twins discordant for bipolar disorder, similar in design to the study mentioned earlier in schizophrenia (Van Oel et al. 2002). In contrast to the discordant schizophrenia twins, in this study we found that the discordant bipolar twin pairs only showed a temporary decline in functioning, and over the longer term did not underperform the healthy control twins. In addition, in contrast to what we found in schizophrenia, the twin who went on to develop bipolar disorder did not do worse in school than his or her unaffected co-twin (Vonk et al. 2012).

Similarly, at illness onset, patients with bipolar disorder, in contrast to those with schizophrenia, do not appear to perform worse than healthy controls. In a study by Zammit et al. (2004), which examined this issue, recent onset bipolar disorder or mania patients performed significantly better than first-episode schizophrenia patients on a broad variety of cognitive tests and only underperformed healthy individuals on two of the sixteen subtests: delayed verbal memory and category fluency. Consistent with the studies reviewed above, the estimate of premorbid intellectual functioning was normal in the bipolar group and decreased in the schizophrenia patients (Zanelli et al. 2010). Finally, a meta-analysis of cognitive functioning in patients with established illness showed that those with bipolar disorder perform significantly better than patients with schizophrenia in almost all cognitive domains, with an effect size of around 0.5. This difference was found for actively ill patients as well as for those in remission (Krabbendam et al. 2005). Taken together, the evidence strongly suggests that low IQ, cognitive underperformance during adolescence

as well as at first presentation of psychosis differentiates schizophrenia from bipolar disorder.

Cognitive Dysfunction as Predictor of General Outcome

The central role of cognitive dysfunction in schizophrenia is solidified by ample evidence that cognitive function is an important determinant of global functional outcome. Although some studies suggest this aspect of the disorder is the strongest predictor of outcome (Bowie et al. 2006), others find that cognitive function is independently, but not necessarily predominantly, predictive of outcome (Mohamed et al. 2008). At any rate, cognitive dysfunction in schizophrenia is unaffected by current pharmacotherapy, which for schizophrenia is almost entirely based on the use of antipsychotic medication. These drugs, which essentially have not been pharmacologically altered since the introduction of chlorpromazine over half a century ago, are indeed effective antipsychotics. However, despite many claims to the contrary, none of these compounds have proven effective in improving cognition in schizophrenia to any meaningful degree. Numerous studies have examined the effect of first- and second-generation antipsychotics on cognitive function in schizophrenia. Although several studies claim improvement in some specific subtests, global cognitive change in large comparative studies in first-episode and chronic schizophrenia rarely reaches an effect size of over 0.3. A meta-analysis of first-generation antipsychotics found an effect size of 0.22 (Mishara and Goldberg 2004), whereas more recent studies that directly compare first- and second-generation antipsychotics have not found differential effects of these drugs with effect sizes of around 0.3 (Keefe et al. 2007; Davidson et al. 2009). However, even this small effect is likely to be no more than practice-related: when healthy individuals are included in the trial design, their improvement on the same tests that are administered to the patients is of a similar effect size as that observed in the patients (Keefe et al. 2008, 2011a). Thus, although cognitive dysfunction is central to outcome in schizophrenia, current pharmacological treatment does not appear to ameliorate it. More promising may be efforts which combine cognitive interventions with rehabilitation programs (Zanelli et al. 2010).

Conclusion

Cognitive underperformance is at the heart of schizophrenia. It constitutes a (genetic) risk factor, precedes the onset of psychosis by many years, continues to worsen after psychosis is established, and determines outcome. Underperformance is broad, evident, and relevant, expressed throughout school in the years prior to the onset of the first psychosis. This underperformance at school constitutes one of the highest hazard ratios found for schizophrenia,

only surpassed by the risk of having a sibling with the illness. Although low IQ at primary school may already constitute a risk factor for schizophrenia, a (further) decline in global cognitive functioning most likely occurs in early puberty, preceding the onset of psychosis by almost a decade. This decline does not halt once the psychosis develops, but appears to progress even further, unstopped by current (pharmacological) treatment methods. Whether this process of cognitive decline prior to psychosis onset is specific to schizophrenia has not been well studied, but it has not been found in bipolar disorder.

What are the consequences of considering schizophrenia primarily and foremost a cognitive instead of a psychotic disorder? First, cognitive decline prior to the onset of psychosis (in most cases retrospectively established) should be part of the diagnosis. This (under)performance should be particularly evident when compared to the intellectual performance of parents and siblings. Second, treatment of cognitive deficits should be central to any guidelines, and are not at present. Third, the whole concept of schizophrenia as an illness which presents with psychosis should be discarded: *schizophrenia presents with cognitive decline*. Fourth, the age of onset of schizophrenia is probably a decade earlier than we now assume.

As proposed in this chapter, schizophrenia is an illness that starts (at least) in early adolescence, around the age of 12–14 years, and is accompanied by a decline in global cognitive functioning relative to healthy peers. As Kraepelin so aptly stated (Kraepelin 1896): *Je weiter sie aber fortschreiten, desto schwerer wird es ihnen mit ihren Kameraden Schritt zu halten* (the more they [affected individuals] continue, the more difficult it is for them to keep up with their peers). This perspective implies that early recognition and prevention programs which focus on (brief and intermittent) psychotic symptoms happen too late in the disease process and, more importantly, fail to address the core aspect of the illness. Indeed, much of the social damage has already occurred once the psychosis finally manifests itself, in late adolescence or young adulthood: a person may have dropped out of school, lost friends, or failed to reach his full potential. Clearly, we have been focusing on the wrong risk phenotype: being prone to psychosis may not constitute the highest risk of developing schizophrenia, but rather the propensity to cognitive decline or intellectual stagnation during adolescence. Just like psychosis (Verdoux and van Os 2002), this phenotype will most likely be much more prevalent in the general population than we now consider it to be. It may be present in many individuals who will not go on to develop psychosis, let alone schizophrenia. Thus, to understand the genetic and environmental influences that lead to schizophrenia, we need to study the interaction between the (genetically mediated) cognitive underperformance during adolescence, and the environmental (and genetic) factors that determine why some of these individuals will eventually develop schizophrenia.

It may be that the boundaries of the disorder that are characterized by progressive cognitive decline prior to and after the onset of psychosis are narrower than those of the illness now defined as schizophrenia. It may be that even

within that (sub)type, various causes will be identified. What is completely clear, however, is that by defining schizophrenia as a psychotic disorder, we have done our patients a disservice. Putting the focus back on cognition may facilitate the search for a cure for the illness that we should, for lack of any better term, have called Kraepelin's Disease.