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Is Schizophrenia a Syndrome of Accelerated Aging?

Brian Kirkpatrick[1,2], Erick Messias[2], Philip D. Harvey[3], Emilio Fernandez-Egea[4], and Christopher R. Bowie[5]

[2]Department of Psychiatry and Health Behavior, Medical College of Georgia, Augusta, GA; [3]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA; [4]Department of Psychiatry, Hospital Clinic, Institut d'Investigacions Biomediques August Pi i Sunyer, Universitat de Barcelona, Barcelona, Spain; [5]Department of Psychiatry, Mount Sinai School of Medicine, New York, NY

Schizophrenia is associated with a number of anatomical and physiological abnormalities outside of the brain, as well as with a decrease in average life span estimated at 20% in the United States. Some studies suggest that this increased mortality is not entirely due to associated causes such as suicide and the use of psychotropic medications. In this article, in order to focus greater attention on the increased mortality associated with schizophrenia, we present a special case of the hypothesis that physiological abnormalities associated with schizophrenia make a contribution to the increased mortality of schizophrenia: specifically, the hypothesis that schizophrenia is a syndrome of accelerated aging. Evidence consistent with this hypothesis comes from several areas. The biological plausibility of the hypothesis is supported by the existence of established syndromes of accelerated aging and by the sharing of risk factors between schizophrenia and other age-related conditions. We propose methods for testing the hypothesis.

Key words: schizophrenia/progeria/aging/epidemiology/mortality

People with schizophrenia have been reported to have an increased prevalence of several anatomical and functional abnormalities in the periphery, compared with controls. These include immunological changes, endocrine abnormalities prior to drug treatment, abnormal fingerprints and palmprints, and other minor physical anomalies from head to toe.[1–16] Some of these await replication, although a meta-analysis strongly confirms the widespread nature and increased prevalence of the minor physical anomalies.[17]

Schizophrenia is also associated with a striking increase in mortality.[18,19] No doubt a number of factors associated with schizophrenia contribute to this mortality, in addition to an increased risk of suicide and accidents: poor health care, poor health habits, and medication side effects, such as the increased risk of diabetes associated with antipsychotic medications, are all serious problems. However, the existence of these problems does not necessarily rule out the possibility that the widespread physiological abnormalities found in schizophrenia also make a contribution, above and beyond the effect of these other environmental and behavioral factors. Despite the potential importance of such a contribution to mortality, the hypothesis that some physiological problem or problem associated with schizophrenia itself, independent of factors such as suicide, poor health care, and the others listed above, has not been seriously considered.

In this article, we present a special case of the more general hypothesis that physiological abnormalities associated with schizophrenia make a contribution to the increased mortality of schizophrenia, specifically, that schizophrenia is a syndrome of accelerated aging. By accelerated aging, we mean that physiological changes throughout the body that are associated with normal aging occur at an earlier age in people with schizophrenia than in the general population. The purpose of presenting this argument is not to argue that this hypothesis must be correct. Rather, our purpose is to focus attention on the mortality of schizophrenia and to foster serious consideration of the more general hypothesis that the physiological abnormalities found in schizophrenia contribute to that mortality.

Several lines of evidence provide a basis for this hypothesis, including studies of the pattern of increased mortality found in schizophrenia, late-life cognitive decline and the lifelong profile of cognitive impairments, other physiological abnormalities, and abnormal brain development schizophrenia that extends beyond the perinatal period. Although these do not provide direct evidence in support of accelerated aging, the biological plausibility of our hypothesis is also supported by the existence of multiple well-established syndromes of accelerated aging and the sharing of risk factors between schizophrenia and other age-related conditions.

[1]To whom correspondence should be addressed; tel: 706-726-9314, fax: 706-721-1793, e-mail: bkirkpatrick2@aol.com.

Mortality

In the United States, people with schizophrenia have an average decrease of approximately 20% in life expectancy compared with the general population.[18] The view that medication side effects, an increased suicide rate, poor health care, and poor health habits account for all the increase in the mortality of schizophrenia is not easily reconciled with some other findings. While the adverse effects of antipsychotics may contribute to overall mortality within schizophrenia, the increased mortality was noted prior to the advent of such drugs.[19] The pattern of mortality within schizophrenia is also remarkable, with an increase in nearly every major category of cause of death,[19] suggesting that a factor with a widespread impact is operating. Moreover, even in a cohort of patients with high-quality psychiatric and medical care, the mortality rate remained twice that of the general population.[20] This evidence suggests that factors associated with schizophrenia, such as medications, poor medical care, and poor health habits, may not account for all the increased mortality that is seen.

Evidence that may appear to refute the hypothesis of accelerated aging comes from studies that have found that cancer may not have an increased mortality in schizophrenia.[19,21] However, other reports have found an increased incidence of cancer in schizophrenia,[22] as well as no difference from the general population[23] (see the review of Grinshpoon et al[24]). Other factors also complicate interpretation of these studies with regard to accelerated aging. Cancer is not a single disease and has several different etiological pathways the confluence in the DNA mutation. Cells that have entered senescence from normal aging are not prone to develop cancer because they have irreversible ''stop'' in the cell cycle. Indeed, the induction of senescence has been suggested as an anticancer therapy.[25] While further study may refute the real incidence of cancer among schizophrenic patients, another possibility that should be considered is that because of the very high rates of suicide and cardiovascular disease patients with schizophrenia may not live long enough, as a group, to show an increase in cancer deaths.

Cognitive Decline

Kraepelin[26] first conceptualized schizophrenia as a disorder of progressive cognitive decline, and the cognitive changes with aging in schizophrenia are also consistent with the hypothesis that schizophrenia is associated with accelerated aging.

Cognitive functioning in schizophrenia presents an intriguing picture where the most substantial deficits seen in the illness across the life span are in processing speed, episodic verbal memory (learning and recall), and high-load information processing, the exact ability domains with the most substantial changes with aging in healthy individuals.[27] In contrast, people with schizophrenia show much more limited deficits compared with healthy people at any point in the life span on tests of crystallized intelligence (the ability to use previously acquired knowledge and experience), such as word recognition reading performance. Cognitive ability domains that are relatively spared in schizophrenia include long-term verbal memory (eg, reading), recognition memory, and verbal abilities that do not require rapid processing, such as naming. These are domains that are also spared from major aging effects in healthy individuals. In fact, some of these ability areas are affected so little in schizophrenia that they are often used to infer premorbid levels of functioning.

Patients with schizophrenia who do show cognitive decline with aging manifest a markedly increased risk for these changes during the period in life (age 65 years and older) when the ability areas described above start to show the greatest change in healthy individuals as well.[28] Thus, the profile of cognitive impairment in schizophrenia at any point in their life could be compared with that of an older healthy individual, one whose brain and subsequent cognitive performance has already experienced the effects of aging. It is clear that in people with schizophrenia, there is little evidence of change in performance associated with aging during the ages of 20–50 years.[28,29] Healthy individuals also show the least decline in cognitive abilities during this same period.

There is considerable evidence that cognitive functioning in schizophrenia changes for the worse during the period of time from the premorbid through prodromal periods, resulting in notable deterioration in performance that occurs over an abbreviated period of time.[30,31] This deterioration, because it occurs in ability areas that are vulnerable to decline with normal aging, could be characterized as a period of ''compressed aging.'' Thus, the decline that occurs within a period of a few months to years affects the same ability areas as normal aging does.

Figure 1, based on previously unpublished data collected by Drs C.R.B. and P.D.H., shows the resemblance between the pattern of cognitive performance in people with schizophrenia and that of older healthy individuals. We selected a subset of the types of tests that are differentially sensitive to the effects of aging in healthy individuals. These include processing speed and episodic memory as examples of abilities that are sensitive to aging in healthy individuals and visual confrontation naming as a test of crystallized intelligence that is not markedly vulnerable to aging influences in healthy individuals.

Healthy individuals 70–80 years of age show performance on tests of processing speed (measured by Wechsler Adult Intelligence Scale-III digit symbol) and episodic verbal memory (measured by Rey Auditory Verbal Learning Test [RAVLT] delayed recall) that are consistent with the performance of 50- to 60-year-old people with schizophrenia,

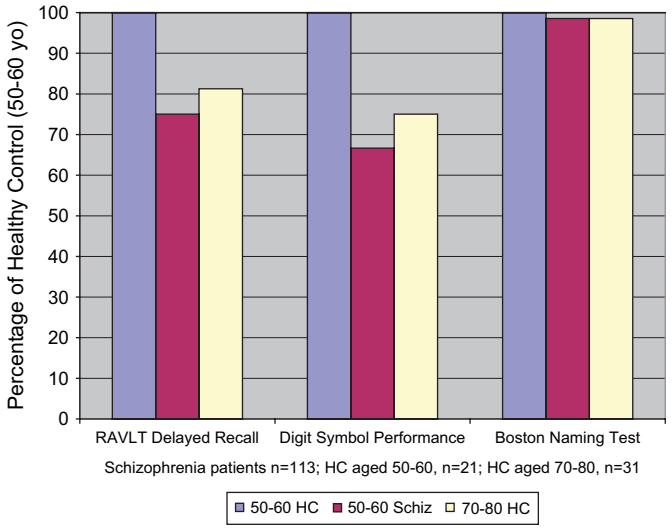

Fig. 1. Performance of Younger and Older Healthy Controls (HCs) and Patients with Schizophrenia on Tests that are Differentially Sensitive to Aging in Healthy Individuals. Specific cognitive decline in schizophrenia and HCs. Schizophrenia patients, $n = 113$; HC aged 50–60 years, $n = 21$; HC aged 70–80 years, $n = 31$.

while 50- to 60-year-old healthy individuals perform markedly better on these 2 tests than do similar aged people with schizophrenia. However, when the performance of all 3 of these groups is compared on a test of verbal confrontation naming, there is remarkably little difference among the groups. Thus, the age-associated burden in cognitive performance on the part of people with schizophrenia appears most prominent on tests where healthy individuals show evidence of reduced performance with aging.

In short, the cognitive changes seen in schizophrenia, even at the time of the first episode, have a strong overlap with those abilities that are vulnerable to the most substantial changes seen in normal aging. People with schizophrenia consistently perform more poorly in aging-vulnerable ability areas than healthy individuals of the same age. Cognitive change in schizophrenia may occur over a shorter time period than normal aging-related changes, with detectable deterioration occurring over abbreviated periods at the time of onset of the illness and in some cases in late life. While the similarly in profile of cognitive abilities affected by schizophrenia and healthy aging does not prove similarity in underlying mechanisms of the change, the possibility of a vulnerable circuit, prone to deterioration with aging and schizophrenia, could be a topic for future investigation.

A major limitation of this line of argument is the small number of studies that compares the cognitive performance in older people with schizophrenia with that of comparison groups. Moreover, many such studies have been cross-sectional, rather than longitudinal, leaving the results vulnerable to bias.

The findings of stable *performance* after the first episode are not necessarily suggestive of stable cognitive *abilities* throughout the rest of the course as measured in previous studies. Most research has found severe cognitive deficits by the time of the first episode as measured by traditional neuropsychological tests, but when patients exhibit this degree of impairment, they are manifesting performance at a level that reduces the sensitivity for detection of further decline because of floor effects for some tests. The more that baseline performance deviates from the average performance of the healthy population, the more difficult it is to both measure and make meaningful sense of performance on these tests. The Wechsler IQ Scale subtests, eg, have a mean of 10 and an SD of 3, so once a patient is 2.5 SD or 3 SD below the mean, a level consistent with the severity seen in people with schizophrenia on many measures by the time of first episode of psychosis, there is limited validity of attempts to measure further decline on these tests due to floor effects. In such a case, attempts to measure declines in cognition will fail not necessarily because of cognitive ability but because of the ability of the instruments employed to measure changes in performance. We[32] found that traditional neuropsychological tests were insensitive to progressive impairments in late-life schizophrenia due to floor effects. However, when we used a scale designed for measuring truly profound cognitive impairment, the Alzheimer Disease Assessment Scale (ADAS)—Late Stage, we found sensitivity to cognitive impairments in patients with Mini-Mental State Examination (MMSE) scores less than 10—in fact, we could differentiate those with MMSE of 1 from those with MMSE of 0. Further, when using tests that are more sensitive to complex information processing demands, we[33,34] found that older schizophrenia outpatients show age-associated impairments into late life. Thus, the supposed stability of cognitive impairment after first episode may have more to do with test selection (relying on neuropsychological tests that were originally designed to distinguish impairment from normal performance, rather than tracking the progression of impairment as is done by scales such as the ADAS-Late Stage) than on what is actually happening to the aging person with schizophrenia.

Thus, what appears to be, from neuropsychological performance on standard clinical measures, nonlinear pattern that entails early decline, followed by stability through much of the course and decline in only a subset of patients and/or on a subset of measures, might simply be the result of our inability to finely measure performance. This issue may be resolved with newer imaging techniques and the development of complex information processing tasks that are sensitive to a wider range of performance than traditional neuropsychological measures.

Metabolic Abnormalities

The evidence that antipsychotic medications increase the risk of obesity, diabetes, and possibly hyperlipidemia is

now quite extensive.[35] However, schizophrenia may also be associated with other metabolic problems, independently of antipsychotic use, specifically diabetes and an increased pulse pressure. Because risk of these problems is strongly associated with increasing age,[36–40] these associations are consistent with the hypothesis that schizophrenia is a disorder of accelerated aging. However, there is a need for replication in these areas.

Diabetes

People with schizophrenia may have an increased risk of diabetes independently of antipsychotic administration, and risk of diabetes increases with age, after controlling for other factors. The evidence for an association between schizophrenia and diabetes include (1) studies predating the advent of antipsychotics, which suggested that impaired glucose tolerance has an increased prevalence within schizophrenia[41–44]; these studies usually lack details on the subjects' characteristics and did not use diagnostic criteria; (2) studies that suggest that schizophrenia is associated with diabetes, whatever the treatment[45,46]; (3) a family study that found an increased prevalence of diabetes in the relatives of schizophrenia probands[47]; and (4) a recent study that found an increased fasting glucose in newly diagnosed, antipsychotic-naive schizophrenia patients, compared with well-matched controls,[48] a finding that has been replicated.[49] Hypercortisolemia may have confounded these differences, while another study, in which the patients and controls were not well matched, did not find impaired glucose tolerance in newly diagnosed, antipsychotic-naive schizophrenia patients.[50] However, we have also found a significant increase in 2-hour glucose concentration in patients with nonaffective psychosis (NAP), compared with controls (Fernandez-Egea, Bernardo, Cheaphy, Griffith, Parellada, Donner, Esmatjes, Conget, George, Stoppler, Kirkpatrick, unpublished data); this difference could not be attributed to greater cortisol in the psychosis group.

Another study found that antipsychotic-naive subjects with schizophrenia had higher plasma insulin and greater insulin resistance than control subjects, as well as lower insulin-like growth factor 1 (IGF1) concentrations.[51] IGF1 is a key hormone in the control of aging.[52,53]

Pulse Pressure

The hypothesis of accelerated aging led us to test the more specific hypothesis that compared with matched controls subjects with psychosis would have an increased pulse pressure. Pulse pressure, defined as the difference between systolic and diastolic blood pressure, reflects arterial elasticity and increases with age[36,39,54,55]; pulse pressure has also been proposed to reflect physiological (as opposed to chronological) aging of the cardiovascular system.[55,56] An elevated pulse pressure has also been associated with insulin resistance, all-causes mortality in the elderly, cardiovascular mortality, kidney disease, risk of dementia, and telomere length, itself thought to be a correlate of biological as opposed to chronological age.[40,55,57–62] We examined pulse pressure in control subjects and newly diagnosed, antipsychotic-naive subjects with NAP. The 2 groups were matched on ethnicity, age, gender, smoking, and body mass index. The NAP group had significantly greater pulse pressure, which could not be attributed to increased systolic or diastolic pressure (Fernandez Egea et al, unpublished data).

Altered Development Extending Beyond the Perinatal Period

The focus of the neurodevelopmental hypothesis of the pathophysiology of schizophrenia is usually on events during gestation. However, the developmental trajectory of people with schizophrenia is abnormal in later stages of life as well. During childhood, they have a distinctive pattern of growth, with low birth weight and a low body mass index.[63] Several studies also suggest the existence of a complex pattern of abnormal cerebral development during adolescence in people with schizophrenia[64] or early course of illness (and possibly only during the early course).[65,66] At least one imaging study has found a greater rate of loss of brain gray matter in schizophrenia subjects than matched controls extending far into adult life.[67] The limited number of studies is an important limitation of this line of argument. We are suggesting that the field tests the hypothesis that there is another aspect of abnormal development: an overall acceleration of the aging process.

Early-Life Risk Factors Shared With Age-Related Conditions

Two other lines of evidence do not provide direct evidence for an association between schizophrenia and accelerated aging but do support the biological plausibility[68] of the hypothesis.

Prototypical Syndromes of Accelerated Aging

The existence of the progerias demonstrates that the rate of aging per se can be thought of as a biological variable on which individuals vary and for which underpinnings can be found. Progerias are the rare prototypal syndrome of accelerated aging. Children with progeria show signs of aging in the early years of their lives, including alopecia, lipodystrophy, and scleroderma-like skin changes.[69] Several well-established progeria syndromes have been described[70,71]; some of these have been traced to single gene mutations. In one form of progeria, Werner Syndrome, patients typically first exhibit their accelerated aging after puberty.[72] It is interesting to note that in a blind comparison, people with schizophrenia were judged to appear to be older than age-matched control subjects.[73]

Shared Risk Factors

Schizophrenia shares some early-life risk factors with other aging-related medical conditions that are associated with an increased mortality. This sharing of etiological factors supports the biological plausibility of an association of schizophrenia with an increased mortality.

Advanced Paternal Age

Advanced paternal age (APA) is a well-replicated risk factor for schizophrenia. Since 1979, there have been 11 publications, with 14 different samples, on the association between APA and schizophrenia. In 12 of these samples, a positive association has been found.[74–84] These studies have included more than 800 000 subjects from several different countries. Potentially confounding factors such as socioeconomic status, family history, social support, parity of the mother, ethnicity, marital status, and age of the mother have all been examined and do not appear to account for the APA effect.

APA has also been associated with several other adverse health outcomes in the offspring, including prostate cancer,[85] an increased risk of malformations of extremities and multisystem abnormalities,[86] autism,[87] and age of onset in Huntington disease and Alzheimer disease.[88–91] APA but not advanced maternal age has also been associated with an increased all-causes mortality in daughters but not sons,[92] a finding that we have replicated.[93] APA is also associated with Hutchinson-Gilford progeria.[94]

Other Shared Risk Factors

In addition to APA, schizophrenia shares some other risk factors and may therefore share some aspects of pathophysiology, with components of the metabolic syndrome, such as diabetes. In addition to family history, as noted above,[47] diabetes and schizophrenia appear to share prenatal risk factors, namely low birth weight[95] and prenatal famine.[63,96–98] Low birth weight, another risk factor for schizophrenia, is also associated with hypertension[99] and hyperlipidemia.[100]

Prenatal stress during the second or early third trimester of pregnancy, due to any of several different causes, appears to confer on the offspring an increased risk of developing schizophrenia later in life, and findings in animals exposed to prenatal stress strengthen this hypothesis (reviewed by Koenig et al[101]). Prenatal developmental problems as risk factors are an important area of research in diabetes and other aspects of the metabolic syndrome.[97,98,102] Genetic factors in mothers and their children may account for some of this variance, but some studies have shown a relationship to the mother's diabetes, and not that of the father, as well as a relationship between adult glucose intolerance and adverse environmental events during gestation.[103] Thus, there appears to risk variance due to the environmental risk factor. Twin studies and studies of dietary manipulations during gestation in animals[104] also suggest shared genes is not a complete explanation of the association between low birth weight and adult diabetes. There are, however, reports of at least one gene that may be associated with risk for both diabetes and schizophrenia, although this association so far lacks replication for both disorders.[105,106]

Discussion

Many factors associated with schizophrenia contribute to the increased mortality and medical comorbidity found in the disorder. Variables such as drug treatment, chronic stress, poor health habits, and an increased risk of suicide should not be ignored when treating the medical problems of people with schizophrenia. However, the hypothesis that the increased mortality found in schizophrenia is adequately explained by these associated factors has not been adequately tested. Moreover, these factors may not adequately account for all the findings we have outlined above, such as the association of schizophrenia with physiological abnormalities in newly diagnosed, antipsychotic-naive patients; the abnormal brain development found in adolescence/early adulthood in people with schizophrenia; and the failure of aggressive medical treatment to bring the mortality of schizophrenia close to normal. In the general case, the alternative hypothesis—that these factors do not completely account for the increased mortality—deserves testing.

The more specific hypothesis of accelerated aging has limitations. Some of the findings we have cited have not to date been replicated, and for many, there are reasonable interpretations other than that of accelerated aging. Nonetheless, this hypothesis warrants testing. It has the advantage of being specific, testable (see below), and parsimonious in the sense that conceptually it accounts for several lines of evidence and it has not been refuted with specific testing. This hypothesis has also led to a specific prediction—that of an increased pulse pressure—that has been borne out.

Testing the Hypothesis

Our hypothesis would suggest that there would be an increase in the prevalence in several aging-related conditions:

- increased insulin resistance,[48]
- hyperlipidemia,[107]
- increased pulse pressure,[56]
- decreased bone density,
- thickening of the eye lens,
- thinning and wrinkling of the skin,
- thinning of the hair,
- decrease in muscle mass.

The hypothesis of accelerated aging would be refuted if there were not, in general, an increased prevalence of these abnormalities, compared with matched control subjects. In testing the hypothesis, it will often be necessary to concentrate on cohorts of newly diagnosed, antipsychotic-naive patients with schizophrenia so that confounding by factors associated with the treatment and progression of the disorder can be minimized.

Another approach to testing the hypothesis would be based on our increasing knowledge of the molecular basis of aging. Several systems appear to be important in the control of aging, including the growth hormone/IGF1 signaling pathway, the telomere, and DNA repair molecules.[108–113] However, with the present state of knowledge, there are limitations to such an approach. These molecular correlates are themselves validated by their association with more conventional measures of aging, such as mortality and the measures in the list just above. Moreover, as a recent review of the molecular mechanisms of aging concluded, "Current evidence supports the concept that there are many roads that can lead to the phenotype (of) aging."[114] If schizophrenia is associated with accelerated aging, it might be associated with one particular "road" and not others.

Confirmation of the hypothesis of accelerated aging could in the long term lead to interventions because the molecular correlates of longevity are increasingly understood. Should it be disconfirmed, a more thorough assessment of the determinants of the increased mortality in schizophrenia should be sought.

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