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Divergent Trajectories of Physical, Cognitive, and Psychosocial Aging in Schizophrenia

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Aging is not a uniform process. In the general population, there is a paradox of aging: age-associated decline in physical and some cognitive functions stands in contrast to an enhancement of subjective quality of life and psychosocial functioning. This paradox is even more striking in people with schizophrenia. Compared with the overall population, individuals with schizophrenia have accelerated physical aging (with increased and premature medical comorbidity and mortality) but a normal rate of cognitive aging, although with mild cognitive impairment starting from premorbid period and persisting throughout life. Remarkably, psychosocial function improves with age, with diminished psychotic symptoms, reduced psychiatric relapses requiring hospitalization and better self-management. Many older adults with schizophrenia successfully adapt to the illness, with increased use of positive coping techniques, enhanced self-esteem and increased social support. Although complete remission is uncommon, most individuals with schizophrenia experience significant improvement in their quality of well-being. Cohort effect and survivor bias may provide a partial explanation for this phenomenon. However, the improvement also may reflect some brain changes that are beneficial for the course of schizophrenia along with neuroplasticity of aging. The proposed hypothesis has several implications. As significant medical morbidity in schizophrenia takes years to develop, studies of changes in sensitive biomarkers of aging during the course of illness may point to new treatments aimed at normalizing the rate of biological aging in schizophrenia. At the same time, effective psychotherapeutic interventions can affect brain structure and function and produce lasting positive behavioral changes in aging adults with schizophrenia.

Key words: psychosis/geriatric/quality of life/psychotherapy/neuropsychological/biomarkers

Introduction

There is a tendency to consider aging as a uniform process. Yet, gerontologists have long known that people age differently and, within the same individual, different organs and systems change with age at varied rates. In the general population, age-associated decline in physical and some cognitive functions stands in sharp contrast to the enhancement of subjective quality of life and psychosocial functioning—the paradox of aging. We have found that most community dwellers over age 60 years do not meet criteria for successful physical aging but have high self-rated successful psychosocial aging.[1] Stone et al[2] studied over 340 000 Gallup poll survey respondents in the United States, ages 18–85 years, and reported that the level of subjective global well-being decreased from the early 20s until age 50 years, but thereafter, improved steadily up through age 85 years. This paradox of aging may be even more striking in people with schizophrenia than in the overall population. In this article, we propose that, in people with schizophrenia, aging affects diverse functions (physical, cognitive, and psychosocial) at different rates. Compared with the population at large, individuals with schizophrenia have accelerated physical decline with age coupled with mild cognitive impairment that exists from early childhood (years prior to the onset of psychosis) and continues throughout life but follows normal rate of age-related changes. Remarkably, psychosocial function improves with age among persons with chronic schizophrenia. Possible explanations, caveats, and implications are discussed below.

Physical Aging

There is evidence for accelerated physical aging[3] in schizophrenia. It has been known since Kraepelin's

that schizophrenia is associated with increased physical comorbidity and 2–12 times higher mortality rate than age-comparable "normal" population. A review of 37 recent articles drawn from 25 countries found the mean standardized mortality rate for all-cause mortality in schizophrenia to be 2.58.[4] The average life span of a person with schizophrenia is 20–25 years shorter than that of an unaffected person. Two-thirds of the excess deaths in schizophrenia are from causes other than suicide. The Antipsychotic Trials of Intervention Effectiveness (CATIE) study reported that 43% of young and middle-aged adults with schizophrenia met criteria for the metabolic syndrome (twice the rate in the general population), and schizophrenia patients had a significant increase in the Framingham 10-year risk of coronary heart disease than matched normal subjects. Our studies[5] found that 60% of middle-aged and older persons with schizophrenia had the metabolic syndrome, and the 10-year risk of coronary heart disease was increased by 79% (95% CI: 50%–107%) relative to the general population.

Inflammation and oxidative stress are implicated in the biology of aging and aging-associated medical disorders[6] as well as in the pathophysiology of schizophrenia. C-reactive protein, a marker of inflammation, is elevated not only in heart disease and the metabolic syndrome but also in schizophrenia.[7] A meta-analysis demonstrated immune activation and an inflammatory syndrome in schizophrenia.[8] Insulin resistance too has been reported to increase with aging and in schizophrenia patients as well. Prolonged or repeated exposure to oxidative stress may accelerate aspects of biological aging. Recent meta-analyses[9] have concluded that schizophrenia is associated with increased oxidative stress markers, including F2-isoprostanes, with greater oxidative stress being associated with longer duration and earlier age of onset of the illness. Telomere length is a robust indicator of biological age.[10] Several studies have reported shorter telomeres in peripheral blood mononuclear cells in persons with schizophrenia compared with healthy subjects.

Possible explanations for rapid physical aging in schizophrenia include the effects of smoking, substance use, sedentary lifestyle, poor health care, and antipsychotic medications (especially the atypical ones). However, a number of studies suggest that the increased medical comorbidity and mortality in schizophrenia may not be solely (or even primarily) attributable to these factors. Smoking and other substance use are considered to be inherent aspects of the neurobiology of the schizophrenia. Sedentary lifestyle and worse health care are mainly consequences of the psychopathology. While many of the atypical antipsychotics definitely increase the risk of metabolic disturbances, several reports have indicated that the greater insulin resistance, shorter telomeres, increased oxidative stress markers, and higher mortality observed in people with schizophrenia are not solely attributable to the use of these medications. Thus, at least some of the excessive comorbidity and mortality in schizophrenia may be a part of the biology of schizophrenia itself. Further research is needed to determine the relative proportions of biological aging caused by schizophrenia per se and that due to associated factors such as smoking, lifestyle, and medications, and whether schizophrenia increases vulnerability to adverse effects of these risk factors.

The accelerated physical aging may not be specific to schizophrenia but may be shared with other serious mental illnesses. For example, several studies have shown accelerated rates of biological aging in depression, as shown by shortened telomere length. In one study, telomere shortening was in direct proportion to the lifetime duration of untreated depression.[11] Also, telomere length in the depressed populations was inversely correlated with F2-isoprostanes and other peripheral oxidative stress markers and with proinflammatory cytokines. These findings suggest that oxidative stress and/or chronic exposure to inflammatory cytokines may form a pathogenic pathway culminating in accelerated cell aging in depression as well as schizophrenia. Because telomere shortening is seen in several conditions that are characterized by increased inflammation or oxidation, accelerated biological aging may be related to inflammatory and oxidative mediators rather than to singular clinical syndromes.

Cognitive Aging

Schizophrenia is a neurodevelopmental disorder in a substantial proportion of cases. There is, however, an ongoing debate about the presence, nature, and course of neurodegeneration in schizophrenia. A number of studies suggest that schizophrenia is associated with mild premorbid cognitive deficits of a magnitude equivalent to about 5 or 10 IQ points (one-third to two-third of an SD below the normative levels), indicating lower cognitive functioning is either a risk factor for schizophrenia or a preclinical reflection of the neuropathology that underlies the disorder itself.[12,13] For instance, Bilder et al[14] conducted a retrospective examination of school transcripts and college aptitude test scores for first-episode schizophrenia patients and healthy comparison subjects and found mild deficits in cognitive function in the schizophrenia group as early as the first grade. There is also some evidence for a modest decline in cognitive functioning between the premorbid to post-onset period.[15] Subsequently, a vast majority of the community-dwelling patients show remarkably stable levels of cognitive functioning.[16] Longitudinal examination of older patients who have been chronically institutionalized most of their adult lives suggests greater than age-expected cognitive decline and conversion to clinical dementia.[17] However, 90% of older persons with schizophrenia live in the community today. We longitudinally followed

142 community-dwelling schizophrenia patients and 209 normal comparison (NC) subjects with annual retesting using a comprehensive neurocognitive battery, from 2 to 10 years, and found no evidence of greater than age-expected cognitive change in any neurocognitive domain.[16] Moreover, there were no differences in stability of cognitive functioning when considered in terms of length of follow-up, changes in severity of psychopathology, or older vs younger adult status. The overall pattern and rate of cognitive changes with aging appear to parallel those seen in the general population (but with a downward shift of the curve indicating greater cognitive impairment at all ages), such as a gradual decline in processing speed throughout the adult life span, decline in some aspects of episodic memory and executive functions, and relative preservation of crystallized verbal knowledge.

Psychosocial Aging

Although Kraepelin conceived of schizophrenia as a dementing disorder with progressive deterioration of global functioning, aging is associated with improvement in psychotic symptoms, reduction in psychiatric relapses requiring hospitalization, and better self-management. A well-known example of a person with schizophrenia who has demonstrated exceptionally high professional and psychosocial functioning after many years of illness is Elyn Saks.[18] While Professor Saks is a standout for her achievements, improved psychosocial functioning characterizes a substantial proportion of middle-aged and older persons with schizophrenia in the community. For most people with schizophrenia, quality of life is a more meaningful outcome than psychiatric symptoms and cognition. Health-related quality of life (HRQOL), defined as a person's self-reported perception of his or her overall well-being, is a way of measuring the impact of a chronic disease on the individual's life and functioning. In a recent study of HRQOL in 486 middle-aged and older community-dwelling patients with schizophrenia, as well as 101 NC subjects, we found schizophrenia was associated with lower physical and mental health HRQOL (as measured with the Medical Outcomes Study 36-Item Short Form (SF-36) Health Survey).[19] There was an age-associated decline in physical HRQOL and improvement in mental HRQOL in both groups, but the difference between the 2 types of HRQOL was significantly greater among schizophrenia patients. Reine et al[20] also found that older patients with schizophrenia had better SF-36 mental HRQOL than did their younger counterparts. Apparent improvement in schizophrenia in later life could be a survivor effect in that the older adults with schizophrenia have avoided suicide and other causes of mortality, although long-term follow-up studies indicate that survivor biases do not fully account for cross-sectional differences. Also, other variables including cognition and physical HRQOL were lower in our older patients, suggesting that our finding was relatively specific to mental HRQOL.

In a qualitative study,[21] 31 of the 32 individuals with schizophrenia over age 50 years reported improvement in the personal impact of symptoms of schizophrenia in later life, after experiencing the greatest degree of disruption and symptom severity in the early years of the illness. The participants described increasing their acceptance and self-management abilities as an active self-motivated process, consonant with the observation of better medication adherence among older vs younger patients. While they were not free of symptoms, they could now engage in strategies that diminished the impact of psychosis, consistent with skills taught in cognitive behavioral therapy. Thus, many older people with schizophrenia had successfully adapted to the illness, and, in addition, some had restructured their social networks to include peers and staff members to compensate for losses in original social networks. Other investigators have reported a stable or increased use of positive coping techniques in persons with schizophrenia over time, and this is associated with enhanced self-esteem and increased social support.

Improved self-management and reduced perceived impact of illness are 2 components of the definition of recovery from schizophrenia. However, there is heterogeneity in terms of recovery. Some people express hopelessness in expectations about the future, despair over lost opportunities during the life span as well as a significant discrepancy between their goals for the future and the current situation. In contrast, others are hopeful about their future and describe the new experience of attaining long-term goals (eg, employment) that had been long derailed by schizophrenia. In a separate study of 145 middle-aged and older people with schizophrenia living independently, we[22] found that 12% were "clinically remitted" and 8% met strict research criteria for sustained remission for periods ranging from 2 to 10 years. Other research has shown that significant predictors of sustained remission include social support, history of marriage, higher cognitive reserve, and early initiation of treatment but neither age nor duration of illness. Thus, although only a small proportion of patients with schizophrenia experience complete and sustained remission, most patients show significant improvements in mental health-related HRQOL as they age.[19,23]

How can we explain improvement in function in later life? Aging is associated with some brain changes that may be beneficial for the course of schizophrenia. Normal age-related neurobiological changes such as reduced activity in the monoaminergic system may produce attenuation in severity of positive symptoms. Older adults have less substance abuse than their younger counterparts. Importantly, contrary to long-held views that brain growth is restricted to childhood, it is now known that neurogenesis and synaptogenesis in discrete brain regions

occur even in later life. Recent research has demonstrated functional and even structural brain changes with psychotherapeutic interventions in people with schizophrenia. Vinogradov et al[24] showed that serum brain-derived neurotrophic factor levels increased steadily in schizophrenia patients participating in 50 hours of computerized auditory training compared with those in patients randomized to a computer game control condition. A recent magnetic resonance imaging (MRI) study[25] of patients with schizophrenia demonstrated that patients who received Cognitive Enhancement Therapy over 2 years showed greater preservation of, and even increase in, gray matter in specific brain regions compared with those who received enriched supportive therapy. These findings suggest the potential for cognitive rehabilitative approaches to positively affect the brain in schizophrenia. Our research group has shown, through randomized controlled trials, that manualized psychosocial interventions including those targeted at functional and social skills, as well as lifestyle interventions and vocational rehabilitation are effective in older persons with schizophrenia. Studies of brain changes with these interventions in older patients have not yet been reported, however.

Synthesis

The available data suggest that, compared with the general population, people with schizophrenia have accelerated physical aging (with increased and premature medical comorbidity and mortality) and a normal rate of cognitive aging, although with mild cognitive impairment starting from premorbid period and persisting throughout life. What is noteworthy is the improvement in psychosocial function with aging. The discrepancy among physical, cognitive, and psychosocial aging may be even more striking in people with schizophrenia than that in the overall population. There are obvious limitations to interpreting such findings. Possible explanations include cohort effects (people born at different time periods represent psychobiosocially diverse cohorts) and survivor bias (the sickest individuals die young so that the people who have survived into old age are a selective subset with strong constitutional resilience). On the other hand, the older individuals with schizophrenia who have had sustained remission are less likely to be identified and to volunteer for research on schizophrenia, thus creating a bias in the opposite direction—ie, underrepresentation of remitted patients in research studies. Furthermore, follow-up studies (including those by Manfred Bleuler and Courtney Harding) have documented progressive improvement in functioning among the patients who received appropriate psychosocial support.

Our hypothesis of divergence in the rates of physical, cognitive, and psychosocial aging in schizophrenia needs to be confirmed in longitudinal prospective studies, using multipronged standardized assessments. Heterogeneity is an inherent characteristic of schizophrenia—therefore, there will not be a single uniform pattern of aging across board. Nonetheless, the suggested variance in physical, cognitive, and psychosocial aging has several implications for interventions. For example, Because significant medical morbidity in schizophrenia takes years to develop, studies of changes in sensitive biomarkers of aging during the course of illness may lead to development of new treatments aimed at normalizing the rate of biological aging in schizophrenia. Indeed, the nonmental (physical) aspects of this serious mental illness may be more critical to the patients' survival in early decades of life. The differential personal trajectories toward or away from recovery in later life point to a need for individually tailored approaches to functional rehabilitation. Psychotherapeutic and rehabilitative interventions can affect brain structure and function, and thus produce positive and lasting behavioral changes in persons with chronic schizophrenia. We should think of schizophrenia, not as a life sentence, but as a serious biological illness with a potential for improvement in later life with appropriate psychobiosocial management.

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Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org. Please see the supplemental material for additional references that were not cited in the article.

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