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Neurodegenerative model of schizophrenia: Growing evidence to support a revisit

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ABSTRACT

Multidimensional progressive declines in the absence of standard biomarkers for neurodegeneration are observed commonly in the development of schizophrenia, and are accepted as consistent with neurodevelopmental etiological hypotheses to explain the origins of the disorder. Far less accepted is the possibility that neurodegenerative processes are involved as well, or even that key dimensions of function, such as cognition and aspects of biological integrity, such as white matter function, decline in chronic schizophrenia beyond levels associated with normal aging. We propose that recent research germane to these issues warrants a current look at the question of neurodegeneration. We propose the view that a neurodegenerative hypothesis provides a better explanation of some features of chronic schizophrenia, including accelerated aging, than is provided by neurodevelopmental hypotheses. Moreover, we suggest that neurodevelopmental influences in early life, including those that may extend to later life, do not preclude the development of neurodegenerative processes in later life, including some declines in cognitive and biological integrity. We evaluate these views by integrating recent findings in representative domains such as cognition and white and gray matter integrity with results from studies on accelerated aging, together with functional implications of neurodegeneration for our understanding of chronic schizophrenia.

1. State of the debate

The progressive nature of schizophrenia was recognized over a hundred years ago and reflected in Emil Kraepelin's diagnostic definition of dementia praecox. However, this clinical observation was not supported by post-mortem research of the neuropathology of schizophrenia. Numerous studies found no histopathologic features of neurodegeneration, the principal pathophysiologic process that characterized brain disorders such as Alzheimer's, Parkinson's and other forms of dementia, which typically included neuropathological features such as gliosis, protein aggregation, ubiquitination or loss of neurons. Having studied neuropathology under Paul Fleischig, and as Chair of the University of Munich department with faculty like Alzheimer and Nissl, Kraepelin was well aware of the inherent contradiction. Moreover, hypotheses about the role of neurodevelopmental abnormalities (i.e., disorders with origins in brain development) in the post-mortem brains of dementia praecox patients (e.g., prefrontal hypoplasia) were articulated by E.E. Southard, the first Director of the Boston Psychopathic Hospital (now called the Massachusetts Mental Health Center) as early as 1915 (Southard, 1915; Zornberg and Tsuang, 1999). Based on clinical features of schizophrenia, however, a mixed picture of clinical decline and clinical improvement (some based on misdiagnosis) prevailed for about two thirds of the 20th century before reports emerged more consistently showing that despite inter-study differences in methodology and perspective (Cohen and Cohen, 1984), significant numbers of individuals with confirmed diagnoses of schizophrenia improved clinically (Bleuler, 1978; Bromet and Fennig, 1999; Ciompi, 1980a; Ciompi, 1980b; Harding et al., 1987; McGlashan, 1988; Ranganathan et al.,

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1992; Tsuang et al., 1979).

By the 1970's and 1980's, the Freudian theories that dominated U.S. psychiatry and the characterization of schizophrenia since the 1950's (e.g., Lidz, Arietti, Sullivan, Reichmann) gave way to the emergence of biologic psychiatry. In parallel with this transition, neurodevelopmental models of schizophrenia that related genetic / biological and environmental characteristics and interactions to trajectories of premorbid vulnerabilities that culminated in the development of psychosis and schizophrenia became ascendant in the 1980's (Bloom, 1993; Crow et al., 1982; Murray and Lewis, 1987; Weinberger, 1987). These models generally included a progressive neurodevelopmental component that accounted for later loss of function in the absence of gliosis, such as abnormalities in pruning or apoptosis (Keshavan et al., 1994). By contrast, neurodegenerative hypotheses remained hamstrung by the continued failure to identify standard biological markers of neurodegeneration or of relentless decline (Birnbaum and Weinberger, 2017; Delisi et al., 1997; El-Mallakh et al., 1991; Lieberman, 1999; Weinberger and McClure, 2002) in chronic schizophrenia. Murray and colleagues have even described the notion of progressive brain disease in chronic schizophrenia (as opposed to progressive processes related to the development of schizophrenia) as a "myth" (Zipursky et al., 2013), though they and others leave the door open for further consideration and newly emergent findings.

While the neurodevelopmental theory remains dominant, the issue remains unsettled for several reasons. Neurodevelopmental models do not readily account for later life features of schizophrenia such as increasing evidence for accelerated aging (Kaufmann et al., 2019; Lin et al., 2021), and to our knowledge, have not been generally extended to do so, though there have been efforts to link early neurodevelopmental effects to later neurodegenerative effects (Kobayashi et al., 2014). Moreover, it remains an open question whether neurodevelopmental effects or other factors, including accelerated aging and neurodegenerative processes, better account for declines in neurobiological, cognitive and clinical functioning that occurs in many patients (Lieberman, 2018; Lieberman et al., 2001), particularly in middle and older ages.

Another problem with the neurodevelopmental theory is the effect of treatment; if treatment can modify the deteriorating trajectory of the illness or prevent the illness in the clinical high risk phase, then the illness may be progressive to some degree (Lieberman, 2018), or a combination of illness and adverse environmental effects. While progressive features are at least compatible with neurodevelopmental effects leading to the development of psychosis, it is unclear what relationship accelerated aging or progressive declines have to neurodevelopmental theory in late life. Reported symptom reductions by antipsychotic medications in aging individuals with schizophrenia (Jeste et al., 2003) are at least as likely to reflect amelioration of an underlying neurodegenerative process as they are to reflect amelioration of an underlying neurodevelopmental one.

In this context, recent findings may help revive the neurodegenerative hypothesis. Steadily increasing evidence of biological dysfunction in schizophrenia such as decreased dendritic spines and arborization and the consequent decreased synaptic and vesicle density and connectivity (Glantz et al., 2006; Lieberman, 1999; Radhakrishan et al., 2021; Smucny et al., 2022) raise new questions about the integrity of biological processes in schizophrenia. Findings such as these emphasize a broader view of neurodegeneration that encompasses a progressive dimension of biological deterioration and functional decline that does not require cell death (Chung et al., 2016; Pino et al., 2014; Rund, 2009) but that does support the possibility of variable outcomes, including changes in outcomes due to treatment or other compensatory mechanisms. However, this evolving view of neurodegeneration has not yet changed opinions about the perceived utility of the neurodegenerative hypothesis (Birnbaum and Weinberger, 2017; Zipursky et al., 2013).

We propose that now is the right time for another look at the data, including recent studies that focus on periods well after the development of psychosis, when most neurodevelopmental effects have likely been expressed. We assume that while adverse neurodevelopmental effects early in life may have life-long consequences (Marenco and Weinberger, 2000), they do not preclude the development of neurodegenerative processes later in life. We contend that evidence about the interaction of chronic schizophrenia with the biological changes that occur during later stages of life, similar to Weinberger's description of the interaction of schizophrenia pathology with normal maturation of brain systems in earlier stages of life, also supports a neurodegenerative hypothesis based on interactions of schizophrenia with aging. Put simply, neurodevelopmental influences during development and maturation do not preclude neurodegenerative processes during aging. We propose that the broad evidence that supports many aspects of the neurodevelopmental model early in life, particularly prior to and soon after the development of psychosis, have less relevance to an array of factors that occur later in life.

We assume further that, similar to the development of schizophrenia (Gottesman and Hanson, 2005; Pries et al., 2020), the course of schizophrenia into middle and older ages would reflect a multifactorial etiology of genetic, epigenetic and environmental influences that would result in heterogenous outcomes. Thus, it is likely that neurodegenerative processes, if present, will affect some aging individuals more than others, as is the case for neurodevelopmental processes. Moreover, conceptualization of schizophrenia as a single disorder with both neurodevelopmental and neurodegenerative components would not be novel: Down's Syndrome is a condition with prominent developmental abnormalities (Patkee et al., 2020) that is also associated with increased prevalence of cognitive decline and dementia after the age of 30 (Ballard et al., 2016). Notably, advances in medical care that have extended the life span of individuals with Down's syndrome (Hendrix et al., 2021) do not contradict its status as a neurodegenerative disorder. While the relationship between the neurodevelopmental hypothesis and the neurodegenerative hypothesis in schizophrenia is not the focus of the current paper, our view of neurodegeneration is consistent with the possibility that early neurodevelopmental deficits contribute to accelerated aging, which subsequently develops a progressively deteriorating course in middle or old age in some people with schizophrenia.

In the remainder of the paper, we will evaluate our view of neurodegeneration in schizophrenia by highlighting recent research about functional and/or biological decline following the development of psychosis. We hypothesize that progressive declines in selected cognitive and white matter domains reflect accelerated aging in at least some people with chronic schizophrenia; that is, they show a neurodegenerative trajectory. Due to limitations of space, we cannot provide a comprehensive review of the relevant literature either for or against our hypothesis, but will emphasize five distinct but interrelated lines of evidence to provide a current, integrated perspective on the question of neurodegenerative processes in schizophrenia.

2. Course and treatment of psychosis

Research in the late 20th and early 21st century which demonstrated that active periods of psychosis in individuals with schizophrenia are associated with illness progression have highlighted the possibility that therapeutic interventions can both alleviate symptoms and modify the course of the illness. In support of this contention, large initiatives such as the International Study of Schizophrenia (ISoS) reported recovery rates as high as 48% after 15 years and 54% after 25 years (Hopper et al., 2007). Findings showing that delays in the initiation of treatment in first-episode schizophrenia were associated with slower treatment response and worse prognoses (Drake et al., 2020; Oliver et al., 2018; Perkins et al., 2005) provide further evidence of the course-modifying effects of treatment. Moreover, patients with first-episode schizophrenia require lower doses of antipsychotic medication (by as much as 50%) and exhibit better treatment response and outcomes compared with patients with chronic, multi-episode schizophrenia (Emsley et al., 2012; Emsley et al., 2013; Lieberman et al., 1993; Lieberman et al., 1996; Sheitman and Lieberman, 1998; Takeuchi et al., 2019; Zipursky et al., 2014), a finding that suggests continued illness progression and the emergence of treatment resistance after the first episode. In the context of treatment response to antipsychotic medications, it is important to note that schizophrenia is not limited to psychosis (Tsuang et al., 2000); it includes negative symptoms, cognitive deficits and biological abnormalities that can persist and worsen during the long course of the illness, suggesting that illness burden can increase over time even in the presence of symptomatic reduction of positive symptoms.

3. Cognition

Reviews of the literature about the course of schizophrenia from the first episode through chronic psychosis emphasize the continued severity and continuity of cognitive deficits (Bonner-Jackson et al., 2010; Harvey, 2014; Heilbronner et al., 2016; Kurtz, 2005; Rajji et al., 2013; Reichenberg and Harvey, 2007; Rund, 1998; Sheffield et al., 2018; Szoke et al., 2008). There is also accumulating evidence about selective declines in cognition as the illness progresses and at least two key questions: First, does cognitive performance decline over time in chronic schizophrenia more rapidly than in healthy individuals? Second, if cognitive performance does decline more rapidly, is it associated with evidence of additional functional or clinical decline?

With respect to the first question, multiple studies show poor performance in selective cognitive functions in schizophrenia, against a background of less severe cognitive deficits in other domains. Deficits in executive functions (e.g., learning, processing speed, organization), which are prominent in all stages of schizophrenia (Giuliano et al., 2012; Stone and Seidman, 2016), are often more pronounced in chronic schizophrenia. For example, a cross sectional study of schizophrenia (n = 87) and healthy controls (n = 94), divided into 3 age groups (20–35; 36–49 and 50–75), showed similar age-related declines in neuropsychological functions except for the oldest group, which showed an accelerated decline in abstraction in patients with schizophrenia (Fucetola et al., 2000). A British study comparing subjects with schizophrenia (n = 36) and nonpsychotic controls (n = 76) from the Northern Finland 1966 Birth Cohort Study assessed when they were 34 years old and re-assessed 9 years later (Kobayashi et al., 2014) found that performance on an abstraction with memory task showed progressive decline in the schizophrenia group compared to controls.

A recent study focused on African-American subjects 20 to 60 years old with either nonaffective (n = 68) or affective (n = 59) psychosis compared to a non-psychotic psychiatric control group (n = 231) (Mollon et al., 2020) reported a broad range of cognitive impairments in the two psychotic groups compared to the non-psychotic controls, with generally more severe impairment in the nonaffective psychotic group. In both psychotic groups there were increasing impairments with age – with the steepest reductions in older subjects – particularly in tests that emphasized executive function (processing speed), as well as in tests of general cognitive ability and working memory.

A 10-year follow-up of 65 individuals with non-affective psychosis, 41 with affective psychosis (mean age of combined psychotic group = 35.1 ± 9.6) and 103 non-psychotic psychiatric controls (mean age = 36.0 ± 10.9) (Zanelli et al., 2019) reported significant declines in the two psychotic groups in IQ, verbal knowledge and memory, but in this instance not in processing speed or other executive dysfunctions. The authors did note, however, in a subsequent letter to the Editor (Zanelli et al., 2020b) that a re-analysis of their data stratified by IQ showed that the subgroup of subjects with baseline IQs above the median showed more widespread cognitive decline at the follow-up than the whole group analyses, including a trend level decline in processing speed (p = 0.089), compared to subjects with baseline IQ below the median, who showed little cognitive decline over the 10-year follow-up. This suggests the possibility that a floor effect muted the expression of processing speed declines in this subsample. In a separate letter to the Editor (Zanelli et al., 2020a), the authors also noted that a further re-analysis of their data showed a significant age by group interaction whereby subjects with schizophrenia showed steeper performance reductions with age in delayed visual recall starting at about the age of 40.

Recently, we studied cognitive aging in schizophrenia using the second phase of the Consortium on the Genetics of Schizophrenia (COGS-2) dataset which includes 1415 patients with schizophrenia or schizoaffective disorder, depressed type, and 1062 healthy community controls (Lee et al., 2020). Patients were under 61 years of age and had a duration of illness of at least 20 years at the time of assessment; the mean (sd) age of females was 47.2 (10.5) years and that of males was 45.9 (11.9). Overall, cognitive performance was reduced in patients compared to controls; age-related cognitive differences were significant but small over the age range assessed. However, in some measures there were larger between group differences with advancing age, including slower performance in social information processing speed and poorer attention/vigilance in patients than in controls. By contrast, patients did not show these age-related effects on tests of verbal or working memory.

A 20-year follow-up study of first-admission patients with schizophrenia spectrum (schizophrenia and schizoaffective disorder), affective and other psychoses assessed six cognitive domains in the patients at year 2 (n = 399) and at year 20 (n = 241) (195 completed both assessments; mean age at year 20 = 49.4 ± 10.1), and in a healthy control group at year 20 (n = 260) (Fett et al., 2020). Performance on most cognitive measures was reduced in year 20 compared to year 2, especially in patients with schizophrenia-spectrum disorders. Compared to controls, the abstraction-executive function measures in patients with schizophrenia and schizoaffective disorder showed the steepest reductions by age, followed by generalized verbal ability.

Given the tendency to treat psychosis in high-income countries as soon as possible, relatively little is known about the cognitive consequences of long-term, untreated psychosis. Our study (Stone et al., 2020) of cognitive functioning in a unique sample of individuals with long-term untreated schizophrenia in rural China (n = 197; mean age = 52.1 ± 11.1; age range = 19–81) found that they performed more poorly than healthy controls (n = 221) on all cognitive measures assessed. Moreover, among these untreated patients – whose duration of psychosis ranged from 1 to 58 years – those with longer durations of psychosis showed poorer cognitive performance on tests adapted from the MATRICS Consensus Cognitive Battery (MCCB) that emphasize executive functions (learning, processing speed and problem solving).

Some studies have reported stable rather than declining executive functioning in chronic schizophrenia. One study administered 8 cognitive tests covering 4 cognitive domains (executive function, attention, total learning and memory) to 16 subjects diagnosed with schizophrenia and 16 age-matched subjects with bipolar disorder at 2 time points about 5 years apart (mean age of the schizophrenia subjects, who had been ill for 15–20 years, at the first assessment was 37.6 ± 4.9) (Burdick et al., 2006). Changes from time 1 to time 2 were not significant for 7 of the 8 tests, supporting the conclusion that cognitive deficits in schizophrenia were stable. However, the one test that did show a significant reduction at time 2 was one of three measures of executive function (Trails B), and a nonsignificant reduction on a second measure of executive function (verbal fluency) would likely have been significant in a larger study.

A second study reporting stability rather than progressive decline involved a follow-up that assessed processing speed and general information knowledge at the index hospitalization and then at 6 time points over a 20-year period in 84 individuals with schizophrenia (mean age at enrollment = 22.8 years), 63 with other psychosis (23.1 years) and 97 with nonpsychotic depression (23.2 years) (Bonner-Jackson et al., 2010). Subjects with schizophrenia performed worse than the other two groups but showed improvement following the index assessment and then stability on both measures. However, there are two methodological issues that make it difficult to assess the validity of this result. First, only two measures of cognitive performance were reported, both involving obsolete subtests from the 1955 version of the Wechsler Adult Intelligence Scale: the conception of what constituted 'general information' and the content of the general information subtest changed substantially between 1955 and 2010; and the content, test design and number of items in the Digit Symbol subtest also changed (Kaufman and Lichtenberger, 2002). Second, the authors reported mean scores for the tests without standard deviations so the variability of test scores over time is unknown.

Some longitudinal studies that do not detect cognitive declines in subjects with schizophrenia do, nevertheless, find much stronger practice effects in control subjects than in patients with schizophrenia (Harvey et al., 2010). Notably, declines in practice effects on neuropsychological tests increase with age in schizophrenia samples (Granholm et al., 2010) and likely contribute to the marked functional declines observed in individuals with schizophrenia over 65 years of age (Harvey, 2014; Harvey and Rosenthal, 2018).

These findings support three tentative conclusions. First, despite heterogeneous outcomes and differences in study designs, test batteries and samples, the majority of studies find that cognitive performances decline at faster rates in schizophrenia than among appropriate control groups, that is, faster than the declines expected due to normal aging. Second, the more rapid declines seen in schizophrenia with age often include specific cognitive domains, while other cognitive domains remain relatively stable. Third, executive dysfunction is a cognitive domain that is often vulnerable to progressive reduction over the course of chronic schizophrenia.

4. Relation to function

Impaired cognition in schizophrenia has long been related to impaired function in major life roles, such as attaining an education, working, and interpersonal communication (Green, 1996; Green et al., 2019; Green et al., 2000; Green et al., 2011). Schizophrenia is also associated with elevated risk of premature mortality (Stone and Keshavan, 2012; Stone et al., 2007) and dementia (Ahearn et al., 2020; Cai and Huang, 2018; Ribe et al., 2015; Shah et al., 2012; Zilkens et al., 2014), which is another condition associated with significant loss of function in life roles. However, the nature of the relationship between impaired cognition and vulnerability to dementing disorders may be stronger for some types of dementia than for others. A postmortem neuropathological analysis of the brains of 100 individuals with schizophrenia 52 to 101 years old at the time of death reported, for example, that 72% had pre-mortem cognitive impairment but only 9% had postmortem evidence of Alzheimer's disease-related pathology (9% of cases); in fact, the prevalence of Alzheimer's disease-related pathology in schizophrenia was similar to that found in age-matched non-schizophrenia controls (Purohit et al., 1998). Wyatt and colleagues reported consistent findings (El-Mallakh et al., 1991).

While findings such as these cast doubt on relationships between schizophrenia and Alzheimer's types dementias specifically, recent studies continue to implicate aging individuals with schizophrenia to other dementing disorders or mixed etiologies. In this context, a large study of U.S. Medicare beneficiaries (n = 18,740) reported that individuals with schizophrenia were at greater risk of dementia than individuals without schizophrenia, even after adjusting for age, sex, race and education (Brown and Wolf, 2018). Similarly, a large prospective population-based study in Denmark of 20,683 individuals with schizophrenia aged 50 or older who were followed for up to 18 years reported double the expected levels of dementia in persons with schizophrenia after controlling for medical comorbidities considered risk factors for dementia (e.g., diabetes mellitus, cardio- and cerebrovascular disorders) (Ribe et al., 2015). Another large, retrospective cohort study using U.S. Medicare data compared 74,170 individuals with schizophrenia over 65 years of age to matched age-by-race/ethnicity cohorts (Black, Hispanic, Non-Hispanic White) without serious mental illness (Stroup et al., 2021); compared to non-schizophrenia controls, individuals with schizophrenia had a higher incidence of dementia (particularly at younger ages), a higher prevalence of dementia (the prevalence among individuals with schizophrenia at age 66 was similar to that of individuals without serious mental illness at age 88), and elevated rates of early mortality.

5. Accelerated aging

Cognitive abilities change throughout life. They strengthen during development (Stone et al., 2016; Waber et al., 2007), plateau in early adulthood and then different cognitive functions (domains) start declining at different ages and rates (Salthouse, 2019). Notably, normal age-related performance decrements in multiple cognitive abilities (e.g., reasoning, memory, and processing speed) are first evident in the 3rd and 4th decades of life (Salthouse, 2009) — not just in middle or old age. The nature and pattern of these cognitive declines in individuals with schizophrenia are similar to the changes seen in healthy individuals, but they typically occur earlier in life (Harvey and Rosenthal, 2018). The functional declines associated with cognitive declines (e.g., deficits in basic and instrumental activities of daily living) that occur in normal aging also occur in schizophrenia, but they start earlier in schizophrenia. This cognitive/functional phenotype in schizophrenia may reflect a combination of overt reductions in cognitive performance compared to healthy controls of the same age (Fett et al., 2020; Lee et al., 2020) and decreased abilities to benefit from rehearsal (such as due to weak practice effects) (Granholm et al., 2010).

Conceptions of accelerated aging over the last 20 years increasingly emphasize the importance of genetic and biological factors that influence both neurodevelopment and ongoing changes throughout the lifespan. The focus has been on identifying and understanding the normative trajectory of biological tissues and mechanisms that change throughout the lifespan. Determining normal age-specific values for these tissues ('molecular aging') in healthy individuals can then be used to estimate the biological aging (in contrast to the chronological aging) of the brain or other organs in cohorts of interest.

In healthy individuals, less than 10% of genes show age-related changes in expression (Sibille, 2013). Evidence from a well-characterized postmortem sample of individuals who died at 13 to 79 years of age showed age-associated differences in human prefrontal cortex in about 7.5% of genes tested (Erraji-Benchekroun et al., 2005), suggesting that biological aging is evident throughout life, as are cognitive (Salthouse, 2019) and other dimensions of aging. Changes in gene expression showed some specificity: up-regulated transcripts were associated with glia and more reactive cellular defenses and inflammation, while down-regulated transcripts were associated with less efficient neuronal signaling. Importantly, about 33% of the genes that have been associated with aging have also been associated with brain disorders, while only 4% of genes that are not associated with aging have been associated with brain disorders (Glorioso et al., 2011).

This issue was explored in a recent study of gene expression in postmortem frontal lobe brain regions (Lin et al., 2021). First, a control sample was used to identify age-related genes and individual molecular ages in one of the frontal regions and then the estimated results were confirmed in the second frontal region. Single nucleotide polymorphisms (SNP) related to gene expression in age-dependent genes and deviation scores from normal values ('delta age') were used with quantitative trait loci (QTL) or genome-wide association study (GWAS) protocols and combined into separate polygenic risk scores (PRS). The estimated PRS were then validated in independent postmortem datasets and clinical samples. The researchers found that individuals with schizophrenia or bipolar disorder had significantly elevated delta (that is, older molecular ages) compared to chronological age-matched controls, but this was not the case in individuals with major depressive disorder. These findings were obtained using SNPs identified using both GWAS and QTL protocols, which suggests that common DNA variations contributed to the older molecular ages in schizophrenia. Moreover, the

GWAS-derived PRS were associated with reduced cognition (lower processing speed and general cognition). These results support the view that accelerated aging and premature mortality are related to interactions between age- and disease-related genes in schizophrenia (and, possibly, other psychiatric or neurological disorders). That is, increased molecular age may provide a partial explanation of accelerated aging and premature mortality in schizophrenia.

Consistent with this point, a postmortem study that assessed DNA methylation in the orbital frontal cortex reported that age-related, differentially methylated regions were enriched in genes associated with risk for schizophrenia, Alzheimer's disease and major depressive disorder. This finding supports the view that DNA methylation modulates the age-related expression of disease-related genes (McKinney et al., 2019), a view supported by the reported relationship of DNA methylation to chronological age (Horvath, 2013) and to mortality risk (Higgins-Chen et al., 2020). The latter study also showed, of note, evidence that the antipsychotic medication clozapine produced male-specific decelerations in aging in several chronological 'clocks' (Higgins-Chen et al., 2020). However, another study that used DNA methylation as an epigenetic clock failed to show accelerated brain aging in schizophrenia (McKinney et al., 2018; Teeuw et al., 2021). This issue is far from settled, but the results support the utility of focusing on factors that modulate the relationship between aging-related genes and disease-related genes.

Another approach to assessing gaps between chronological age and biological integrity uses machine learning methods to estimate brain age based on features identified by structural brain imaging. In one large study (n = 45,615) of individuals 3 to 96 years of age, brain age was estimated based on cortical thickness, area and volume, and a set of cerebellar and other subcortical volume variables (Kaufmann et al., 2019). Age, gender and scanning site were among the variables included in the models. Significant brain age gaps (i.e., brain age–chronological age) were identified in several disorders for which cohorts were available; the largest gaps were in dementia (Cohen's $d = 1.03$), multiple sclerosis ($d = 0.74$) and schizophrenia ($d = 0.51$). However, the weighted mean age of participants in the 7 cohorts with schizophrenia included in the study was in the mid 30's, so it was not possible to assess whether the brain age gap increased with age. Nevertheless, other findings reported in the study were consistent with those reported in the postmortem gene expression studies discussed above (Lin et al., 2021): 1) regional brain analyses showed that the largest brain age gap occurred in the frontal lobe for individuals with schizophrenia ($d = 0.70$); 2) the brain age gap was associated with functional changes including lower Global Assessment of Functioning Scale scores.

6. Gray and white matter deterioration

Neurobiological abnormalities are well documented in schizophrenia, both before and after the development of psychosis (Collin et al., 2020; Di Biase et al., 2021; Dietsche et al., 2017; Erkol et al., 2020; Lewandowski et al., 2020; Stone and Seidman, 2016). Importantly, the limited number of longitudinal studies about this issue report progressive neurobiological deterioration (Lewandowski et al., 2020).

6.1. Gray matter deterioration

Gray matter abnormalities such as volume deficits and cortical thinning are prominent both before and after the development of psychosis (Del Re et al., 2021; Dietsche et al., 2017; Lewandowski et al., 2020), are related to neuropil loss documented post-mortem (Selemon and Goldman-Rakic, 1999) and in some instances, to neuropsychological deficits (Nestor et al., 2020). These deficits also exceed normal age-related atrophy, as shown in a recent study of 326 individuals diagnosed with schizophrenia or schizoaffective disorder and 197 healthy controls 20–65 years of age (Cropley et al., 2017). Specifically, the rate of gray matter volume loss was accelerated in the illness up to middle age, while from age 50 and onward, the rate of loss slowed to a degree not significantly different from comparison subjects. The finding of accelerated gray matter loss up to middle age that plateaus thereafter, in contrast to a deficit in white matter that progressively worsens with age at a constant rate (Cropley et al., 2017), raises a question of the relative roles of gray versus white matter degeneration in symptom and functional domains that will need to be addressed in future studies.

Regionally, the most significant gray matter loss has been reported in medial prefrontal cortex, hippocampus, and thalamus (Cropley et al., 2017; Dietsche et al., 2017). A cross-sectional causal network analysis study based on duration of illness found that as a function of disease duration, reduction in gray matter volume began in the thalamus and progressed to the frontal lobe, and then to the temporal and occipital cortices (Jiang et al., 2018). A cautionary note in assessing putative neurodegeneration by means of gray matter changes is the potential confound of cumulative exposure to antipsychotic medication and its potential effects on gray matter volumes (Dietsche et al., 2017; Liu et al., 2020).

6.2. White matter deterioration

The relation of white matter deterioration to middle and older age (Cropley et al., 2017) is of particular interest. Studies over the last decade have linked white matter function (assessed using measures of fractional anisotropy and dysconnectivity) (Fitzsimmons et al., 2013; Fornito et al., 2012) to normal aging, to age-related decline in non-psychotic disorders (Dev et al., 2017), and to the likelihood of accelerated aging in in schizophrenia (Cetin-Karayumak et al., 2020; Cropley et al., 2017; Di Biase et al., 2021; Kochunov et al., 2013; Kochunov and Hong, 2014; Wang et al., 2021). White matter function is related to core cognitive deficits in schizophrenia such as processing speed, working memory (Kochunov et al., 2017; Roalf et al., 2013), and general cognitive ability (Holleran et al., 2020); it is also related to other abnormalities and disorders associated with degeneration such as pro-inflammatory cytokines (Rodrigue et al., 2019), myelin and oligodendroglial deterioration (Roussos and Haroutunian, 2014; Takahashi et al., 2011), and Alzheimer's disease (Kochunov et al., 2021).

A study of white matter integrity during normal aging in 203 subjects 20 to 84 years of age showed greater annualized percentage declines in fractional anisotropy (FA) in frontal lobes (−0.5%, ± 0.9 standard deviations) than in the other three lobes, with most age-related declines starting in the 40s (Sexton et al., 2014). Proposed models of accelerated aging based on lower FA differentiate patterns of white matter maturation and decline that are likely attributable to (1) developmental etiologies (i.e., reduced integrity throughout the lifespan), (2) developmental / maturational etiologies (i.e., premature peak maturity followed by plateau or declines; i.e., neither a neurodevelopmental nor a neurodegenerative course), or (3) accelerated aging (i.e., normal development until the onset of the disorder, followed by age-related accelerated declines (Kochunov and Hong, 2014).

Consistent with these models, age-related patterns of white matter reduction have been reported in the last few years. A study of 600 patients with schizophrenia and 492 healthy controls 14 to 65 years of age showed lower whole brain FA across the lifespan and earlier peak maturation in the patient group (Cetin-Karayumak et al., 2020). Specific fiber tracts stratified by region showed evidence of neurodevelopmental, maturational and/or accelerated aging (considered here as a likely neurodegenerative process). Tracts associated with accelerated decline involved long-range association fibers and callosal fibers.

Another recent study (Wang et al., 2021) analyzed data from 107 healthy controls using a machine learning approach to estimate 'white matter brain age' and then used these results to estimate differences between chronological age and brain age (i.e., delta age) in a second sample of 107 healthy controls and in 166 subjects with schizophrenia. Among patients and controls 30 years of age or older, delta age was significantly higher in patients than controls, but there was no significant difference in delta age between patients and controls under 30 years of age. Moreover, after adjustment for gender and chronological age, delta age correlated significantly with working memory and processing speed.

7. Summary

These findings support the view that at least some significant domains of function in schizophrenia, including aspects of cognition and white matter integrity, show progressive reductions with increasing chronological age after the onset of psychosis. We propose that declines associated with accelerated aging reflect a neurodegenerative process. We also suggest that accelerated brain aging contributes to early mortality.

As we noted in the first section of the paper, our suggestion of a neurodegenerative process that underlies an array of interactions between schizophrenia and aging does not directly address how neurodevelopmental and neurodegenerative mechanisms might interact with each other, or the extent to which neurodegenerative mechanisms, like neurodevelopmental mechanisms, are heterogeneous. However, based on our findings and those of others working on chronic schizophrenia, we contend that the neurodegenerative hypothesis is better able to account for increasing age-related dysfunction in chronic schizophrenia than the neurodevelopmental hypothesis. However, as we illustrated with the example of Down's Syndrome, the question of neurodegeneration and neurodevelopment in schizophrenia need not be framed as either one or the other; both may be operative at different times or even at the same time.

There are several useful implications of a neurodegenerative perspective based on accelerated aging in mid-life to later-life schizophrenia, some of which may reduce heterogeneity and improve predictions of clinical outcomes. First, clinical or cognitive stability or even improvement with treatment, may not be sufficient to predict outcomes in the absence of biomarker (e.g., white matter integrity) confirmation. This is analogous to other (non-schizophrenic) aging individuals with good or even superior performances on tests of memory who still accumulate dementia-related neuropathology (Cook et al., 2017; Dang et al., 2019). Thus, individuals with schizophrenia who respond well to initial treatment or otherwise show clinical improvement are still vulnerable to subsequent accelerated decline. Second, our formulation of a degenerative process influenced by combinations of genetic, epigenetic and environmental variables in an unknown percentage of individuals with chronic schizophrenia suggests that the cognitive and biological decline leading to some forms of dementia reflects active, ongoing processes. While this view does not preclude early effects such as neurodevelopmentally low levels of cognitive ability (Seidman et al., 2013) and/or low levels of education (Yokomizo, 2020) from contributing to life-long low levels of cognitive reserve, we propose that interactions of schizophrenia with aging also contribute independently to poor outcomes such as dementia and shortened life spans. Although we focus here on the question of neurodegenerative processes in chronic schizophrenia and treat broader etiological questions somewhat agnostically, we recognize the significance of this issue for both early assessment and intervention.

The extent to which either of these implications are correct will require a shift in our conceptualization of the life course of schizophrenia. Further confirmation of this updated neurodegenerative perspective on the etiology and course of schizophrenia will require additional studies aimed at improving our understanding of the nature and extent of accelerated aging in cognition, white matter function and other functional and biological domains. We also need to improve our understanding of the inter-relationship between age-related changes in these different domains. Such studies, together with more longitudinal designs and cutting-edge multidimensional investigations such as the use of PET or MRS scans to assess neurotransmission disturbances or synaptic deficits and the continued study of long-term untreated psychosis (Laruelle et al., 1996; Merritt et al., 2021; Radhakrishan et al., 2021; Stone et al., 2020; Wijtenburg et al., 2017) will refine our understanding of neurodegenerative processes in schizophrenia further in coming years. They might even lift the neurodegenerative hypothesis from the realm of myth.

CRediT authorship contribution statement

Dr. Stone wrote the initial draft and takes responsibility for the general integrity of the review. Drs. Phillips, Yang, Kegeles, Susser and Lieberman contributed to the conceptualization of the manuscript and to the review and approval of the final manuscript.

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Declaration of competing interest

All authors declare that they have no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three (3) years of beginning the work submitted that could inappropriately influence, or be perceived to influence, their work.

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References

Ahearn, E.P., Szymanski, B.R., Chen, P., Sajatovic, M., Katz, I.R., McCarthy, J.F., 2020. Increased risk of dementia among veterans with bipolar disorder or schizophrenia receiving care in the VA health system. Psychiatr. Serv. 71, 998–1004.
Ballard, C., Mobley, W., Hardy, J., Williams, G., Corbett, A., 2016. Dementia in Down's syndrome. Lancet Neurol. 15, 622–626.
Birnbaum, R., Weinberger, D.R., 2017. Genetic insights into the neurodevelopmental origins of schizophrenia. Nat. Rev. Neurosci. 18, 727–740.
Bleuler, M., 1978. The Schizophrenic Disorders: Long-term Patient and Family Studies. Yale University Press, New Haven, CT.
Bloom, F.E., 1993. Advancing a neurodevelopmental origin for schizophrenia. Arch. Gen. Psychiatry 50, 224–227.
Bonner-Jackson, A., Grossman, L.S., Harrow, M., Rosen, C., 2010. Neurocognition in schizophrenia: a 20-year multi-follow-up of the course of processing speed and stored knowledge. Compr. Psychiatry 51, 471–479.
Bromet, E.J., Fennig, S., 1999. Epidemiology and natural history of schizophrenia. Biol. Psychiatry 46, 871–881.
Brown, M.T., Wolf, D.A., 2018. Estimating the prevalence of serious mental illness and dementia diagnoses among medicare beneficiaries in the health and retirement survey. Res. Aging 40, 668–686.
Burdick, K.E., Goldberg, J.F., Harrow, M., Faull, R.N., Malhotra, A.K., 2006. Neurocognition as a stable endophenotype in bipolar disorder and schizophrenia. J. Nerv. Ment. Dis. 194, 255–260.
Cai, L., Huang, J., 2018. Schizophrenia and risk of dementia: a meta-analysis study. Neuropsychiatr. Dis. Treat. 14, 2047–2055.
Cetin-Karayumak, S., Di Biase, M.A., Chunga, N., Reid, B., Somes, N., et al., 2020. White matter abnormalities across the lifespan of schizophrenia: aharmonized multi-site diffusion MRI study. Mol. Psychiatry 25, 3208–3219.
Chung, J.K., Nakajima, S., Plitman, E., Iwata, Y., Uy, D., et al., 2016. Beta-amyloid burden is not associated with cognitive impairment in schizophrenia: a systematic review. Am. J. Geriatr. Psychiatr. 24, 923–939.
Ciompi, L., 1980a. Catamnestic long-term study on the course of life and aging of schizophrenics. Schizophr. Bull. 6, 606–618.
Ciompi, L., 1980b. The natual history of schizophrenia in the long term. Br. J. Psychiatry 136, 413–420.
Cohen, P., Cohen, J., 1984. The clinician's illusion. Arch. Gen. Psychiatry 41, 1178–1183.

Collin, G., Seidman, L.J., Keshavan, M.S., Stone, W.S., Qi, Z., et al., 2020. Functional connectome organization predicts conversion to psychosis in clinical high-risk youth from the SHARP program. Mol. Psychiatry 25 (10), 2431–2440.

Cook, A.H., Sridhar, J., Ohm, D., Rademaker, A., Mesulam, M.-M., et al., 2017. Rates of cortical atrophy in adults 80 years and older with superior vs average episodic memory. JAMA 317, 1373–1375.

Cropley, V.L., Klauser, P., Lenroot, R.K., Bruggerman, J., Sundram, S., et al., 2017. Accelerated gray and white matter deterioration with age in schizophrenia. Am. J. Psychiatr. 174, 286–295.

Crow, T.J., Cross, A.J., Johnstone, E.C., Owen, F., 1982. Two syndromes in schizophrenia and their pathogenesis. In: Henn, F.A., Nasrallah, H.A. (Eds.), Schizophrenia as a Brain Disease. Oxford University Press, p. 196.

Dang, C., Harrington, K.D., Lim, Y.Y., Ames, D., Hassenstab, J., et al., 2019. Superior memory reduces 8-year risk of mild cognitive impairment and dementia but not amyloid β-associated cognitive decline in older adults. Arch. Clin. Neuropsychol. 34, 585–598.

Del Re, E.C., Stone, W.S., Bouix, S., Seitz, J., Zeng, V., et al., 2021. Baseline cortical thickness reductions in clinical high risk for psychosis: brain regions associated with conversion to psychosis versus non-conversion as assessed at one-year follow-up in the Shanghai-at-risk-for-psychosis (SHARP) study. Schizophr. Bull. 47, 562–574.

Delisi, L.E., Sakuma, M., Tew, W., Kushner, M., Hoff, A.L., Grimson, R., 1997. Schizophrenia as a chronic active brain process: a study of progressive brain structural change subsequent to the onset of schizophrenia. Psychiatry Res. 74, 129–140.

Dev, S.I., Nguyen, T.T., McKenna, B.S., Sutherland, A.N., Bartsch, H., et al., 2017. In: Steeper Slope of Age-related Changes in White Matter Microstructure and Processing Speed in Bipolar Disorder, 25, pp. 744–752.

Di Biase, M.A., Cetin-Karayumak, S., Lyall, A.E., Zalesky, A., Cho, K., et al., 2021. White matter changes in psychosis risk relate to development and are not impacted by the transition to psychosis. Mol. Psychiatry 26 (11), 6833–6844. In this issue.

Dietsche, B., Kircher, T., Falkenberg, I., 2017. Structural brain changes in schizophrenia at different stages of the illness. A selective review of longitudinal magnetic resonance imaging studies. Aust. N. Z. J. Psychiatry 51, 500–508.

Drake, R.J., Husain, N., Marshall, M., Lewis, S.W., Tomenson, B., et al., 2020. Effect of delaying treatment of first-episode psychosis on symptoms and social outcomes: a longitudinal analysis and modelling study. Lancet Psychiatry 7, 602–610.

El-Mallakh, R.S., Kirch, D.G., Shelton, R., Fan, K.-J., Pezeshkpour, G., et al., 1991. The nucleus basalis of meynert, senile placques, and intellectual impairment in schizophrenia. J. Neuropsychiatry Clin. Neurosci. 3, 383–386.

Emsley, R., Nuamah, I., Hough, D., Gopal, S., 2012. Treatment response after relapse in a placebo-controlled maintenance trial in schizophrenia. Schizophr. Res. 138, 29–34.

Emsley, R., Oosthuizen, P., Koen, L., Niehaus, D., Martinez, L., 2013. Comparison of treatment response in second-episode versus first-episode schizophrenia. J. Clin. Psychopharmacol. 33, 80–83.

Erkol, C., Cohen, T., Chouinard, V.-A., Lewandowski, K.E., Du, F., Ongur, D., 2020. White matter measures and cognition in schizophrenia. In: Front. Psychiatry, 11.

Erraji-Benchekroun, L., Underwood, M.D., Arango, V., Galfalvy, H., Pavlidis, P., et al., 2005. Molecular aging in human prefrontal cortex is selective and continuous throughout adult life. Biol. Psychiatry 57, 449–458.

Fett, A.K.J., Velthorst, E., Reichenberg, A., Ruggero, C.J., Callahan, J.L., et al., 2020. Long-term changes in cognitive functioning in individuals with psychotic disorders. JAMA Psychiatry 77, 387–396.

Fitzsimmons, J., Kubicki, M., Shenton, M.E., 2013. Review of functional and anatomical brain connectivity findings in schizophrenia. Curr. Opin. Psychiatry 26, 172–187.

Fornito, A., Zalesky, A., Pantelis, C., Bullmore, E.T., 2012. Schizophrenia, neuroimaging and connectomics. NeuroImage 62, 2296–2314.

Fucetola, R., Seidman, L.J., Kremen, W.S., Faraone, S.V., Goldstein, J.M., Tsuang, M.T., 2000. Age and neuropsychological function in schizophrenia: a decline in executive abilities beyond that observed in healthy volunteers. Biol. Psychiatry 48, 137–146.

Giuliano, A.J., Li, H., Mesholam-Gately, R., Sorenson, S.M., Woodberry, K.A., Seidman, L. J., 2012. Neurocognition in psychosis risk syndrome: a quantitative and qualitative review. Curr. Pharm. Des. 18, 399–415.

Glantz, L.A., Gilmore, J.H., Lieberman, J.A., Jarskog, L.F., 2006. Apoptotic mechanisms and the synaptic pathology of schizophrenia. Schizophr. Res. 81, 47–63.

Glorioso, C., Oh, S., Douillard, G.G., Sibille, E., 2011. Brain molecular aging, promotion of neurological disease and modulation by Sirtuin5 longevity gene polymorphism. Neurobiol. Dis. 41, 279–290.

Gottesman, I.I., Hanson, D.R., 2005. Human development: biological and genetic processes. Annu. Rev. Psychol. 56, 263–286.

Granholm, E., Link, P., Fish, S., Kraemer, H., Jeste, D.V., 2010. Age-related practice effects across longitudinal neuropsychological assessments in older people with schizophrenia. Neuropsychology 24, 616–624.

Green, M.F., 1996. What are the functional consequences of neurocognitive deficits in schizophrenia. Am. J. Psychiatr. 153, 321–330.

Green, M.F., Horan, W.P., Lee, J., 2019. Nonsocial and social cognition in schizophrenia: current evidence and future directions. World Psychiatry 18, 146–161.

Green, M.F., Kern, R.S., Braff, D.L., Mintz, J., 2000. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophr. Bull. 26, 119–136.

Green, M.F., Schooler, N.R., Kern, R.S., Frese, F., Granberry, W., et al., 2011. Evaluation of co-primary measures for clinical trials of cognition enhancement in schizophrenia. Am. J. Psychiatr. 168, 400–407.

Harding, C.M., Brooks, G.W., Ashikaga, T., Strauss, J.S., Breier, A.A., 1987. The Vermont longitudinal study of persons with severe mental illness-I: methodology, study sample, and overall status 32 years later. Am. J. Psychiatr. 144, 718–726.

Harvey, P.D., 2014. What is the evidence for changes in cognition and functioning over the lifespan in patients with schizophrenia? J. Clin. Psychiatry Suppl. 2, 34–38.

Harvey, P.D., Reichenberg, A., Bowie, C.R., Patterson, T.L., Heaton, R.K., 2010. The course of neuropsychological performance and functional capacity in older patients with schizophrenia: influences of previous history and long-term institutional stay. Biol. Psychiatry 67, 933–939.

Harvey, P.D., Rosenthal, J.B., 2018. Cognitive and functional deficits in people with schizophrenia: evidence for accelerated or exaggerated aging? Schizophr. Res. 196, 14–21.

Heilbronner, U., Samara, M., Leucht, S., Falkai, P., Schulze, T.G., 2016. The longitudinal course of schizophrenia across the lifespan: clinical cognitive and neurobiological aspects. Harv. Rev. Psychiatry 24, 118–128.

Hendrix, J.A., Amon, A., Abbeduto, L., Agiovlasitis, S., Alsaied, T., et al., 2021. Opportunities, barriers, and recommednations in down syndrome research. Transl. Sci. Rare Dis. 5, 99–129.

Higgins-Chen, A., Boks, M., Vinkers, C., Kahn, R., Levine, M., 2020. Schizophrenia and epigenetic aging biomarkers: increased mortality, reduced cancer risk, and unique clozapine effects. Biol. Psychiatry 88, 224–235.

Holleran, L., Kelly, S., Alloza, C., Agartz, I., Andreassen, O.A., et al., 2020. The relationship between white matter microstructure and general cognitive ability in patients with schizophrenia and healthy participants in the ENIGMA consortium. Am. J. Psychiatr. 177, 537–547.

Hopper, K., Harrison, G., Wanderling, J.A., 2007. An overview of course and outcome in ISoS in recovery from schizophrenia. An international perspective. A report from the WHO collaborative project. In: Hopper, K., Harrison, G., Janca, A., Sartorius, N. (Eds.), The International Study of Schizophrenia, pp. 23–38. Geneva, Switzerland.

Horvath, S., 2013. DNA methylation age of human tissues and cell types. Genome Biol. 14, 115–120.

Jeste, D.V., Barak, Y., Madhusoodanan, S., Grossman, F., Gharabawi, G., 2003. An international multisite double-blind trial of the atypical antipsychotic risperdone and olanzapine in 175 elderly patients with chronic schizophrenia. Am. J. Geriatr. Psychiatr. 11, 638–647.

Jiang, Y., Luo, C., Li, X., Duan, M., He, H., et al., 2018. Progressive reduction in gray matter in patients with schizophrenia assessed with MR imagingby using causal network analysis. Radiology 287, 729.

Kaufman, A.S., Lichtenberger, E.O., 2002. In: Assessing Adolescent and Adult Intelligence. Allyn & Bacon, Boston, Massachusetts, pp. 61–95.

Kaufmann, T., van der Meer, D., Doan, N.T., Schwarz, E., Lund, M.J., et al., 2019. Common brain disorders are associated with heritable patterns of apparent aging of the brain. Nat. Neurosci. 22, 1617–1623.

Keshavan, M., Anderson, S., Pettegrew, J.W., 1994. Is schizophrenia due to excessive synaptic pruning in the prefrontal cortex? The Feinberg hypothesis revisited. J. Psychiatr. Res. 28 (3), 239–265.

Kobayashi, H., Isohanni, M., Jaaskelainen, E., Miettunen, J., Veijola, J., et al., 2014. Linking the developmental and degenerative theories of schizophrenia: association between infant development and adult cognitive decline. Schizophr. Bull. 40, 1319–1327.

Kochunov, P., Coyle, T.R., Rowland, L.M., Jahanshad, N., Thompson, P.M., et al., 2017. Association of white matter with core cognitive deficits in patients with schizophrenia. JAMA Psychiatry 74, 958–966.

Kochunov, P., Glahn, D.C., Rowland, L.M., Olvera, R.L., Winkler, A., et al., 2013. Testing the hypothesis of accelerated cerebral white matter aging in schizophrenia and major depression. Biol. Psychiatry 73, 482–491.

Kochunov, P., Hong, L.E., 2014. Neurodevelopmental and neurodegenerative models of schizophrenia: white matter at the center stage. Schizophr. Bull. 40, 721–728.

Kochunov, P., Zavaliangos-Petropulu, A., Jahanshad, N., Thompson, P.M., Ryan, M.C., et al., 2021. A white matter connection of schizophrenia and Alzheimer's disease. Schizophr. Bull. 47, 197–206.

Kurtz, M.M., 2005. Neurocognitive impairment across the lifespan in schizophrenia: an update. Schizophr. Res. 74, 15–26.

Laruelle, M., Abi-Dargham, A., van Dyke, C.H., Gil, R., D'Souza, D.C., et al., 1996. Single photon emission computerized tomography imaging of amphetamine-indiced dopamine release in drug-free schizophrenic subjects. Proc. Natl. Acad. Sci. U. S. A. 93, 9235–9240.

Lee, J., Green, M.F., Nuechterlein, K.H., Swerdlow, N.R., Greenwood, T.A., et al., 2020. The effects of age and sex on cognitive impairment in schizophrenia: findings from the consortium on the genetics of schizophrenia (COGS) study. PLoS One 15, e0232855.

Lewandowski, K.E., Bouix, S., Ongur, D., Shenton, M.E., 2020. Neuroprogression across the early course of psychosis. J. Psychiatry Brain Sci. 5, e200002.

Lieberman, J., Jody, D., Geisler, S., Alvir, J., Loebel, A., et al., 1993. Time course and biologic correlates of treatment response in first-episode schizophrenia. Arch. Gen. Psychiatry 50, 369–376.

Lieberman, J.A., 1999. Is schizophrenia a neurodegenerative disorder? A clinical and neurobiological perspective. Biol. Psychiatry 46, 729–739.

Lieberman, J.A., 2018. Disease modifying effects of antipsychotic drugs in schizophrenia: a clinical and neurobiological perspective. World Psychiatry 17, 163–165.

Lieberman, J.A., Alvir, J.M., Koreen, A., Geisler, S., Chakos, M., et al., 1996. Psychobiologic correlates of treatment response in schizophrenia. Neuropsychopharmacology 14, 13S–21S.

Lieberman, J.A., Perkins, D., Belger, A., Chakos, M., Jarskog, F., et al., 2001. The early stages of schizophrenia: speculations on pathogenesis, pathophysiology and therapeutic approaches. Biol. Psychiatry 50, 884–897.

Lin, C.-W., Chang, L.-C., Ma, T., Oh, H., French, B., et al., 2021. Older molecular brain age in severe mental illness. Mol. Psychiatry 26 (7), 3646–3656.

Liu, N., Xiao, Y., Zhang, W., Tang, B., Zeng, J., et al., 2020. Characteristics of gray matter alterations in never-treated and treated chronic schizophrenic patients. Transl. Psychiatry 10, 136.
Marenco, S., Weinberger, D.R., 2000. The neurodevelopmental hypothesis of schizophrenia: following a trail of evidence from cradle to the grave. Dev. Psychopathol. 12, 501–527.
McGlashan, T.H., 1988. A selective review of recent north american long-term followup studies of schizophrenia. Schizophr. Bull. 14, 515–542.
McKinney, B.C., Lin, C.-W., Rahman, T., Oh, H., Lewis, D.A., et al., 2019. DNA methylation in the human frontal cortex reveals a putative mechanism for age-by-disease interactions. TranslationalPsychiatry 39.
McKinney, B.C., Lin, H., Ding, Y., Lewis, D.A., Sweet, R.A., 2018. DNA methylation age is not accelerated in in brain or blood of subjects with schizophrenia. Schizophr. Res. 196, 39–44.
Merritt, K., McGuire, P.K., Egerton, A., Aleman, A.A., et al., Investigators H-MiS, 2021. Association of age, antipsychotic medication, and symptom severity in schizophrenia with proton magnetic resonance spectroscopy brain glutamate level: a mega-analysis of individual participant level data. JAMA Psychiatry 78, 667–681.
Mollon, J., Mathias, S.R., Knowles, E.E.M., Rodrigue, A., Koenis, M.M.G., et al., 2020. Cognitive impairment from early to middle adulthood in patients with affective and nonaffective psychotic disorders. Psychol. Med. 50, 48–57.
Murray, R.M., Lewis, S.W., 1987. Is schizophrenia a neurodevelopmental disorder? Br. Med. J. (Clin. Res. Educ.) 295, 681–682.
Nestor, P.G., Forte, M., Ohtani, T., Levitt, J.J., Newell, D.T., et al., 2020. Faulty executive attention and memory interactions in schizophrenia: prefrontal gray matter volume and neuropsychological impairment. Clin. EEG Neurosci. 51, 267–274.
Oliver, D., Davies, C., Crossland, G., Lim, S., Gifford, G., et al., 2018. Can we reduce the duration of untreated psychosis? A systematic review and meta-analysis of controlled interventional studies. Schizophr. Bull. 44, 1362–1372.
Patkee, P.A., Baburamani, A.A., Kyriakopoulou, V., Davidson, A., Avini, E., et al., 2020. Early alterations in cortical and cerebellar regional brain growth in down syndrome: an in vivo fetal and neonatal assessment. Neuroimage Clin. 25, 102139.
Perkins, D.O., Gu, H., Boteva, K., Lieberman, J.A., 2005. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta analysis. Am. J. Psychiatr. 162, 1785–1804.
Pino, O., Guilera, G., Gomez-Benito, J., Najas-Garcia, A., Rufian, S., Rojo, E., 2014. Neurodevelopment or neurodegeneration: review of theories of schizophrenia. Actas Esp. Psiquiatr. 42, 185–195.
Pries, L.-K., Dal Ferro, G.A., van Os, J., Delespaul, P., Kenis, G., et al., 2020. Examining the independent and joint effects of genomic and exposomic liabilities for schizophrenia across the psychosis spectrum. Epidemiol. Psychiatr. Sci. 29, e182.
Purohit, D.P., Perl, D.P., Haroutunian, V., Powchick, P., Davidson, M., Davis, K.L., 1998. Alzheimer disease and related neurodegenerative diseses in elderly patients with schizophrenia: a postmortem neuropathologic study of 100 cases. Arch. Gen. Psychiatry 55, 205–211.
Radhakrishan, R., Skosnik, P.D., Ranganathan, M., Naganawa, M., Toyonaga, T., et al., 2021. In vivo evidence of lower synaptic vescile density in schizophrenia. Mol. Psychiatry 26 (12), 7690–7698.
Rajji, T.K., Voineskos, A.N., Butters, M.A., Miranda, D., Arenovich, T., et al., 2013. Cognitive performance of individuals with schizophrenia across seven decades: a study using the MATRICS consensus cognitive battery. Am. J. Geriatr. Psychiatr. 21, 108–118.
Ranganathan, M., Bromet, E.J., Eaton, W.W., Pato, C., Schwartz, J.E., 1992. The natural course of schizophrenia: a review of first-admission studies. Schizophr. Bull. 18, 185–207.
Reichenberg, A., Harvey, P.D., 2007. Neuropsychological impairments in schizophrenia: integration of performance-based and brain imaging findings. Psychol. Bull. 133, 833–858.
Ribe, A.R., Larsen, T.M., Charles, M., Katon, W., Fenfer-Gron, M., et al., 2015. Long-term risk of dementia in persons with schizophrenia: a danish population-based cohort study. JAMA Psychiatry 72, 1095–1101.
Roalf, D.R., Ruparel, K., Verma, R., Elliott, M.A., Gur, R.E., Gur, R.C., 2013. White matter organization and neurocognitive perfomance variability in schizophrenia. Schizophr. Res. 143, 172–178.
Rodrigue, A.L., Knowles, E.E.M., Mollon, J., Mathias, S.R., Koenis, M.M.G., et al., 2019. Evidence for genetic correlation between human cerebral white matter microstructure and inflammation. Hum. Brain Mapp. 40, 4180–4191.
Roussos, P., Haroutunian, V., 2014. Schizophrenia: susceptibility genes and oligodendroglial and myelin related abnormalities. Front. Cell. Neurosci. 8.
Rund, B.R., 1998. A review of longitudinal studies of cognitive functions in schizophrenia patients. Schizophr. Bull. 24, 425–435.
Rund, B.R., 2009. Is schizophrenia a neurodegenerative disorder? Nordic J. Psychiatry 63, 196–201.
Salthouse, T.A., 2009. When does age-related cognitive decline begin? Neurobiol. Aging 30, 507–514.
Salthouse, T.A., 2019. Trajectories of normal cognitive aging. Psychol. Aging 34, 17–24.
Seidman, L.J., Cherkerzian, S., Goldstein, J.M., Agnew-Blais, J., Tsuang, M.T., Buka, S.L., 2013. Neuropsychological performance and family history in children at age 7 who develop adult schizophrenia or biploar psychosis in the New England family studies. Psychol. Med. 43, 119–131.
Selemon, L.D., Goldman-Rakic, P.S., 1999. The reduced neuropil hypothesis: a circuit based model of schizophrenia. Biol. Psychiatry 45, 17–25.
Sexton, C.E., Walhovd, K.B., Storsve, A.B., Tamnes, C.K., Westlye, L.T., et al., 2014. Accelerated changes in white matter microstructure during aging: a longitudinal diffusion tensor imaging study. J. Neurosci. 34, 15425–15436.
Shah, J.N., Qureshi, S.U., Jawaid, A., Schulz, P.E., 2012. Is there evidence for late cognitive decline in chronic schizophrenia? Psychiatry Q. 83, 127–144.
Sheffield, J.M., Karcher, N.R., Barch, D.M., 2018. Cognitive deficits in psychotic disorders: a lifespan perspective. Neuropsychol. Rev. 28, 509–533.
Sheitman, B., Lieberman, J.A., 1998. The natural history and pathophysiology of treatment resistant schizophrenia. J. Psychiatr. Res. 32, 143–150.
Sibille, E., 2013. Molecular aging of the brain, neuroplasticity, and vulnerability to depression and other brain-related disorders. Dialogues Clin. Neurosci. 15, 53–65.
Smucny, J., Dienel, S.J., Lewis, D.A., Carter, C.S., 2022. Mechanisms underlying dorsolateral prefrontal cortex contributions to cognitive dysfunction in schizophrenia. Neuropharmacology 47 (1), 292–308.
Southard, E.E., 1915. On the topographical distribution of cortex lesions and anomalies in dementia praecox, with some account of their functional significance. Am. J. Insanity 71, 603–671.
Stone, W.S., Cai, B., Liu, X., Grivel, M.M., Yu, G., et al., 2020. Association between the duration of untreated psychosis and selective cognitive performance in community-dwelling individuals with chronic untreated schizophrenia in rural China. JAMAPsychiatry 77, 1–11.
Stone, W.S., Keshavan, M.S., 2012. Medical co-morbidity in schizophrenia. In: Marcopulos, B., Giuliano, A.J. (Eds.), The Neuropsychology of Schizophrenia, pp. 159–180.
Stone, W.S., Mesholam-Gately, R.I., Giuliano, A.J., Woodberry, K.A., Addington, J., et al., 2016. Healthy adolescent performance on the MATRICS cognitive consensu battery (MCCB): developmental data from two samples of healthy volunteers. Schizophr. Res. 172, 106–113.
Stone, W.S., Roe, A.H., Tsuang, M.T., 2007. In: Marneros, A., Akiskal, A.H. (Eds.), Overlapping of the Spectra: Physical Comorbidity between Schizophrenia and Affective Disorders in the Overlap of Affective and Schizophrenic Spectra. Cambridge University Press, Cambridge, pp. 207–223.
Stone, W.S., Seidman, L.J., 2016. Neuropsychological and structural imaging endophenotypes in schizophrenia. In: Cicchetti, D. (Ed.), Developmental Psychopathology. John Wiley & Sons, Inc., Hoboken, New Jersey, pp. 931–965.
Stroup, T.S., Olfson, M., Huang, C., Wall, M.M., Goldberg, T., et al., 2021. Age-specific prevalence and incidence of dementia diagnoses among older US adults with schizophrenia. JAMAPsychiatry 78.
Szoke, A., Trandafir, A., Dupont, M.E., Meary, A., Schurhoff, F., Leboyer, M., 2008. Longitudinal studies of cognition in schizophrenia:meta-analysis. Br. J. Psychiatry 192, 248–257.
Takahashi, N., Sakurai, T., Davis, K.L., Buxbaum, J.D., 2011. Linking oligodendrocyte and myelin dysfunction to neurocircuitry abnormalitiesin schizophrenia. Prog. Neurobiol. 93, 13–24.
Takeuchi, H., Siu, C., Remington, G., Fervaha, G., Zipursky, R.B., et al., 2019. Does relapse contribute to treatment resistance? Antipsychotic response in first- vs. Second-episode schizophrenia. Neuropsychopharmacology 44, 1036–1042.
Teeuw, J., Ori, A.P.S., Brouwer, R.M., de Zwarte, S.M.C., Schnack, H.G., et al., 2021. Accelerated aging in the brain, epigenetic aging in blood, and polygenic risk for schizophrenia. Schizophr. Res. 231, 189–197.
Tsuang, M.T., Stone, W.S., Faraone, S.V., 2000. Towards reformulating the diagnosis of schizophrenia. Am. J. Psychiatr. 147, 1041–1050.
Tsuang, M.T., Woolson, R.F., Fleming, J.A., 1979. Long-term outcome of major psychoses. I. Schizophrenia and affective disorders compared with psychiatrically symptom-free surgical conditions. Arch. Gen. Psychiatry 36, 1295–1301.
Waber, D.P., De Moor, C., Forbes, P.W., Almli, C.R., Botteron, K.N., et al., 2007. The NIH MRI study of normal brain development: performance of a population based sample of healthy children aged 6 to 18 years on a neuropsychological battery. J. Int. Neuropsychol. Soc. 13, 729–746.
Wang, J., Kochunov, P., Sampath, H., Hatch, K.S., Ryan, M.C., et al., 2021. White matter brain aging in relationship to schizophrenia and its cognitive deficit. Schizophr. Res. 230, 9–16.
Weinberger, D.R., 1987. Implications of normal brain development for the pathogenesis of schizophrenia. Arch. Gen. Psychiatry 44, 660–669.
Weinberger, D.R., McClure, R.K., 2002. Neurotoxicity, neuroplasticity, and magnetic imaging morphology. Arch. Gen. Psychiatry 59, 553–558.
Wijtenburg, S.A., Wright, S.N., Korenic, S.A., Gaston, F.E., Ndubuizu, N., 2017. Altered glutamate and regional cerebral blood flow levels in schizophrenia: a (1)H-MRS and pCASL study. Neuropharmacology 42, 562–571.
Yokomizo, J.E., 2020. SuperAgers in low-education setting: how to assess cognition. Int. Psychogeriatr. 32, 165–167.
Zanelli, J., Mollon, J., Sandin, S., Morgan, C., Dazzan, P., et al., 2019. Cognitive change in schizophrenia and other psychoses in the decade following the first epidsode. Am. J. Psychiatr. 176, 811–819.
Zanelli, J., Mollon, J., Sandin, S., Reichenberg, A., 2020. Are visual memory deficits in recent-onset psychosis degenerative? Response to Smucny et al. American Journal of Psychiatry 177, 356–357.
Zanelli, J., Mollon, J., Sandin, S., Reichenberg, A., 2020. Further analysis of cognitive change in schizophrenia and other psychoses in the decade following the first episode: response to Panayiotou et al. American Journal of Psychiatry 177, 354–355.
Zilkens, R.R., Bruce, D.G., Duke, J., Spilsbury, K., Semmens, J.B., 2014. Severe psychiatric disorders in mid-life and risk of dementia in late-life(age 65–84 years: a population based case-control study. Curr. Alzheimer Res. 11, 681–693.

Zipursky, R.B., Menezes, N.M., Streiner, D.L., 2014. Risk of symptom recurrence with medication discontinuation in first-episode psychosis: a systematic review. Schizophr. Res. 152, 408–414.
Zipursky, R.B., Reilly, T.J., Murray, R.M., 2013. The myth of schizophrenia as a progressive brain disease. Schizophr. Bull. 39, 1363–1372.
Zornberg, G., Tsuang, M.T., 1999. Elmer E. Southard, M.D. 1876-1920. American Journal of Psychiatry 156, 1263.