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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

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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.

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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 & 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 & Cohen 1984), significant numbers of individuals with confirmed diagnoses of schizophrenia improved clinically (Bleuler 1978, Bromet & Fennig 1999, Ciompi 1980a, Ciompi 1980b, Harding et al 1987, McGlashan 1988, Ranganathan et al 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 & 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 & Weinberger 2017, Delisi et al 1997, El-Mallakh et al 1991, Lieberman 1999, Weinberger & 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 2020), 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. Steadliy 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 2021) 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 & 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 & 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 & 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 <u>and</u> 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 & 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 & 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 & 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 1,415 patients with schizophrenia or schizoaffective disorder, depressed type, and 1,062 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 & 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 & 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 & Keshavan 2012, Stone et al 2007) and dementia (Ahearn et al 2020, Cai & 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 & 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 & 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 2020). 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 2020): 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 2018, Di Biase et al 2021, Dietsche et al 2017, Erkol et al 2020, Lewandowski et al 2020, Stone & Seidman 2016). Importantly, the limited number of longitudinal studies about this issue report progressive neurobiological deterioration (Lewandowski et al 2020).

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 & 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).

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 & 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 & 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 & 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 different 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.

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References

Ahearn EP, Szymanski BR, Chen P, Sajatovic M, Katz IR, McCarthy JF. 2020. Increased risk of dementia among veterans with bipolar disorder or schizophrenia receiving care in the VA health system. Psychiatric Services 71: 998–1004 [PubMed: 32517643]

Ballard C, Mobley W, Hardy J, Williams G, Corbett A. 2016. Dementia in Down's Syndrome. Lancet Neurology 15: 622–26 [PubMed: 27302127]

Birnbaum R, Weinberger DR. 2017. Genetic insights into the neurodevelopmental origins of schizophrenia. Nature Reviews Neuroscience 18: 727–40 [PubMed: 29070826]

Bleuler M 1978. The Schizophrenic Disorders: Long-term Patient and Family Studies. New Haven, CT: Yale University Press.

Bloom FE. 1993. Advancing a neurodevelopmental origin for schizophrenia. Archives of General Psychiatry 50: 224–27 [PubMed: 8439244]

Bonner-Jackson A, Grossman LS, Harrow M, Rosen C. 2010. Neurocognition in schizophrenia: a 20-year multi-follow-up of the course of processing speed and stored knowledge. Comprehensive Psychiatry 51: 471–79 [PubMed: 20728003]

Bromet EJ, Fennig S. 1999. Epidemiology and natural history of schizophrenia. Biological Psychiatry 46: 871–81 [PubMed: 10509170]

Brown MT, Wolf DA. 2018. Estimating the prevalence of serious mental illness and dementia diagnoses among Medicare beneficiaries in the Health and Retirement Survey. Research on Aging 40: 668–86 [PubMed: 28856968]

Burdick KE, Goldberg JF, Harrow M, Faull RN, Malhotra AK. 2006. Neurocognition as a stable endophenotype in bipolar disorder and schizophrenia. Journal of Nervous and Mental Disease 194: 255–60 [PubMed: 16614546]

Cai L, Huang J. 2018. Schizophrenia and risk of dementia: a meta-analysis study. Neuropsychiatric Disease and Treatment 14: 2047–55 [PubMed: 30147318]

Cetin-Karayumak S, Di Biase MA, Chunga N, Reid B, Somes N, et al. 2020. White matter abnormalities across the lifespan of schizophrenia: aharmonized multi-site diffusion MRI study. Molecular Psychiatry 25: 3208–19 [PubMed: 31511636]

Chung JK, 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. American Journal of Geriatric Psychiatry 24: 923–39

Ciompi L 1980a. Catamnestic long-term study on the course of life and aging of schizophrenics. Schizophrenia Bulletin 6: 606–18 [PubMed: 7444392]

Ciompi L 1980b. The natual history of schizophrenia in the long term. British Journal of Psychiatry 136: 413–20

Cohen P, Cohen J. 1984. The clinician's illusion. Archives in General Psychiatry 41: 1178–83

Collin G, Seidman LJ, Keshavan MS, Stone WS, Qi Z, et al. 2018. Functional connectome organization predicts conversion to psychosis in clinical high-risk youth from the SHARP program Molecular Psychiatry

Cook AH, 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: 1373–75 [PubMed: 28384819]

Cropley VL, Klauser P, Lenroot RK, Bruggerman J, Sundram S, et al. 2017. Accelerated gray and white matter deterioration wtih age in schizophrenia. American Journal of Psychiatry 174: 286–95 [PubMed: 27919183]

Crow TJ, Cross AJ, Johnstone EC, Owen F. 1982. Two syndromes in schizophrenia and their pathogenesis In Schizophrenia as a Brain Disease, ed. Henn FA, Nasrallah HA, pp. 196-: Oxford University Press

Dang C, Harrington KD, Lim YY, 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. Archives of Clinical Neuropsychology 34: 585–98 [PubMed: 30272115]

Del Re EC, Stone WS, 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. Schizophrenia Bulletin 47: 562–74 [PubMed: 32926141]

Delisi LE, Sakuma M, Tew W, Kushner M, Hoff AL, Grimson R. 1997. Schizophrenia as a chronic active brain process: a study of progressive brain structural change subsequent to the onset of schizophrenia. Psychiatry Research 74: 129–40 [PubMed: 9255858]

Dev SI, Nguyen TT, McKenna BS, Sutherland AN, Bartsch H, et al. 2017. Steeper Slope of Age-Related Changes in White Matter Microstructure and Processing Speed in Bipolar Disorder. 25: 744–52

Di Biase MA, Cetin-Karayumak S, Lyall AE, 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. Molecular Psychiatry

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. Australian and New Zealand Journal of Psychiatry 51: 500–08 [PubMed: 28415873]

Drake RJ, Husain N, Marshall M, Lewis SW, 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: 602–10 [PubMed: 32563307]

El-Mallakh RS, Kirch DG, Shelton R, Fan K-J, Pezeshkpour G, et al. 1991. The nucleus basalis of Meynert, senile placques, and intellectual impairment in schizophrenia. Journal of Neuropsychiatry and Clinical Neurosciences 3: 383–86 [PubMed: 1821257]

Emsley R, Nuamah I, Hough D, Gopal S. 2012. Treatment response after relapse in a placebo-controlled maintenance trial in schizophrenia. Schizophrenia Research 138: 29–34 [PubMed: 22446143]

Emsley R, Oosthuizen P, Koen L, Niehaus D, Martinez L. 2013. Comparison of treatment response in second-episode versus first-episode schizophrenia. Journal of Clinical Psychopharmacology 33: 80–83 [PubMed: 23277247]

Erkol C, Cohen T, Chouinard V-A, Lewandowski KE, Du F, Ongur D. 2020. White matter measures and cognition in schizophrenia. Frontiers in Psychiatry 11

Erraji-Benchekroun L, Underwood MD, Arango V, Galfalvy H, Pavlidis P, et al. 2005. Molecular aging in human prefrontal cortex is selective and continuous throughout adult life. Biological Psychiatry 57: 449–58

Fett AKJ, Velthorst E, Reichenberg A, Ruggero CJ, Callahan JL, et al. 2020. Long-term changes in cognitive functioning in individuals with psychotic disorders. JAMA Psychiatry 77: 387–96 [PubMed: 31825511]

Fitzsimmons J, Kubicki M, Shenton ME. 2013. Review of functional and anatomical brain connectivity findings in schizophrenia. Current Opinion in Psychiatry 26: 172–87 [PubMed: 23324948]

Fornito A, Zalesky A, Pantelis C, Bullmore ET. 2012. Schizophrenia, neuroimaging and connectomics. Neuroimage 62: 2296–314 [PubMed: 22387165]

Fucetola R, Seidman LJ, Kremen WS, Faraone SV, Goldstein JM, Tsuang MT. 2000. Age and Neuropsychological Function in Schizophrenia: A Decline in Executive Abilities Beyond that Observed in Healthy Volunteers. Biological Psychiatry 48: 137–46 [PubMed: 10903410]

Giuliano AJ, Li H, Mesholam-Gately R, Sorenson SM, Woodberry KA, Seidman LJ. 2012. Neurocognition in psychosis risk syndrome: a quantitative and qualitative review. Current Pharmaceutical Design 18: 399–415 [PubMed: 22239571]

Glantz LA, Gilmore JH, Lieberman JA, Jarskog LF. 2006. Apoptotic mechanisms and the synaptic pathology of schizophrenia. Schizophrenia Research 81: 47–63 [PubMed: 16226876]

Glorioso C, Oh S, Douillard GG, Sibille E. 2011. Brain molecular aging, promotion of neurological disease and modulation by Sirtuin5 longevity gene polymorphism. Neurobiology of Disease 41: 279–90 [PubMed: 20887790]

Gottesman II, Hanson DR. 2005. Human development: biological and genetic processes. Annual Review of Psychology 56: 263–86

Granholm E, Link P, Fish S, Kraemer H, Jeste DV. 2010. Age-related practice effects across longitudinal neuropsychological assessments in older people with schizophrenia. Neuropsychology 24: 616–24 [PubMed: 20804250]

Green MF. 1996. What are the functional consequences of neurocognitive deficits in schizophrenia. American Journal of Psychiatry 153: 321–30 [PubMed: 8610818]

Green MF, Horan WP, Lee J. 2019. Nonsocial and social cognition in schizophrenia: current evidence and future directions. World Psychiatry 18: 146–61 [PubMed: 31059632]

Green MF, Kern RS, Braff DL, Mintz J. 2000. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophrenia Bulletin 26: 119–36 [PubMed: 10755673]

Green MF, Schooler NR, Kern RS, Frese F, Granberry W, et al. 2011. Evaluation of co-primary measures for clinical trials of cognition enhancement in schizophrenia. American Journal of Psychiatry 168: 400–07 [PubMed: 21285142]

Harding CM, Brooks GW, Ashikaga T, Strauss JS, Breier AA. 1987. The Vermont longitudinal study of persons with severe mental illness-I: Methodology, study sample, and overall status 32 years later. American Journal of Psychiatry 144: 718–26 [PubMed: 3591991]

Harvey PD. 2014. What is the evidence for changes in cognition and functioning over the lifespan in patients with schizophrenia? Journal of Clinical Psychiatry Supplement 2: 34–38 [PubMed: 24919170]

Harvey PD, Reichenberg A, Bowie CR, Patterson TL, Heaton RK. 2010. The course of neuropsychological performance and functional capacity in older patients with schizophrenia: Influences of previous history and long-term institutional stay Biological Psychiatry 67: 933–39 [PubMed: 20202624]

Harvey PD, Rosenthal JB. 2018. Cognitive and functional deficits in people with schizophrenia: Evidence for accelerated or exaggerated aging? Schizophrenia Research 196: 14–21 [PubMed: 28506706]

Heilbronner U, Samara M, Leucht S, Falkai P, Schulze TG. 2016. The longitudinal course of schizophrenia across the lifespan: clinical cognitive and neurobiological aspects. Harvard Review of Psychiatry 24: 118–28 [PubMed: 26954596]

Hendrix JA, Amon A, Abbeduto L, Agiovlasitis S, Alsaied T, et al. 2021. Opportunities, barriers, and recommednations in down syndrome research. Translational Sciences of Rare Diseases 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. Biological Psychiatry 88: 224–35 [PubMed: 32199607]

Holleran L, Kelly S, Alloza C, Agartz I, Andreassen OA, et al. 2020. The relationship between white matter microstructure and general cognitive ability in patients with schizophrenia and healthy participants in the ENIGMA Consortium. American Journal of Psychiatry 177: 537–47 [PubMed: 32212855]

Hopper K, Harrison G, Wanderling JA. 2007. An overview of course and outcome in ISoS In Recovery from Schizophrenia. An International Perspective. A Report from the WHO Collaborative Project, the International Study of Schizophrenia, ed. Hopper K, Harrison G, Janca A, Sartorius N, pp. 23–38. Geneva, Switzerland

Horvath S 2013. DNA methylation age of human tissues and cell types. Genome Biology 14: 115–20 [PubMed: 23657273]

Jeste DV, 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. American Journal of Geriatric Psychiatry 11: 638–47

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 [PubMed: 29668409]

Kaufman AS, Lichtenberger EO. 2002. Assessing Adolescent and Adult Intelligence. pp. 61–95. Boston, Massachusetts: Allyn & Bacon.

Kaufmann T, van der Meer D, Doan NT, Schwarz E, Lund MJ, et al. 2019. Common brain disorders are associated with heritable patterns of apparent aging of the brain. Nature Neuroscience 22: 1617–23 [PubMed: 31551603]

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. Schiophrenia Bulletin 40: 1319–27

Kochunov P, Coyle TR, Rowland LM, Jahanshad N, Thompson PM, et al. 2017. Association of white matter with core cognitive deficits in patients with schizophrenia. JAMA Psychiatry 74: 958–66 [PubMed: 28768312]

Kochunov P, Glahn DC, Rowland LM, Olvera RL, Winkler A, et al. 2013. Testing the hypothesis of accelerated cerebral white matter aging in schizophrenia and major depression. Biological Psychiatry 73: 482–91 [PubMed: 23200529]

Kochunov P, Hong LE. 2014. Neurodevelopmental and neurodegenerative models of schizophrenia: white matter at the center stage. Schizophrenia Bulletin 40: 721–28 [PubMed: 24870447]

Kochunov P, Zavaliangos-Petropulu A, Jahanshad N, Thompson PM, Ryan MC, et al. 2021. A white matter connection of schizophrenia and Alzheimer's disease. Schizophrenia Bulletin 47: 197–206 [PubMed: 32681179]

Kurtz MM. 2005. Neurocognitive impairment across the lifespan in schizophrenia: an update. Schizophrenia Research 74: 15–26 [PubMed: 15694750]

Laruelle M, Abi-Dargham A, van Dyke CH, Gil R, D'Souza DC, et al. 1996. Single photon emission computerized tomography imaging of amphetamine-indiced dopamine release in drug-free schizophrenic subjects. Proceedings of the National Academy of Science of the United States of America 93: 9235–40

Lee J, Green MF, Nuechterlein KH, Swerdlow NR, Greenwood TA, 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 [PubMed: 32401791]

Lewandowski KE, Bouix S, Ongur D, Shenton ME. 2020. Neuroprogression across the early course of psychosis. Journal of Psychiatry and Brain Science 5: e200002 [PubMed: 32258424]

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. Archives of General Psychiatry 50: 369–76 [PubMed: 8098203]

Lieberman JA. 1999. Is schizophrenia a neurodegenerative disorder? A clinical and neurobiological perspective. Biological Psychiatry 46: 729–39 [PubMed: 10494440]

Lieberman JA. 2018. Disease modifying effects of antipsychotic drugs in schizophrenia: a clinical and neurobiological perspective. World Psychiatry 17: 163–65 [PubMed: 29856557]

Lieberman JA, Alvir JM, Koreen A, Geisler S, Chakos M, et al. 1996. Psychobiologic correlates of treatment response in schizophrenia. Neuropsychopharmacology 14: 13S–21S [PubMed: 8866739]

Lieberman JA, Perkins D, Belger A, Chakos M, Jarskog F, et al. 2001. The early stages of schizophrenia: speculations on pathogenesis, pathophysiology and therapeutic approaches. Biological Psychiatry 50: 884–97 [PubMed: 11743943]

Lin C-W, Chang L-C, Ma T, Oh H, French B, et al. 2020. Older molecular brain age in severe mental illness. Molecular Psychiatry

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. Translational Psychiatry 10: 136 [PubMed: 32398765]

Marenco S, Weinberger DR. 2000. The neurodevelopmental hypothesis of schizophrenia: following a trail of evidence from cradle to the grave. Development and Psychopathology 12: 501–27 [PubMed: 11014750]

McGlashan TH. 1988. A selective review of recent North American long-term followup studies of schizophrenia. Schizophrenia Bulletin 14: 515–42 [PubMed: 3064280]

McKinney BC, Lin C-W, Rahman T, Oh H, Lewis DA, et al. 2019. DNA methylation in the human frontal cortex reveals a putative mechanism for age-by-disease interactions. Translational Psychiatry 39

McKinney BC, Lin H, Ding Y, Lewis DA, Sweet RA. 2018. DNA methylation age is not accelerated in in brain or blood of subjects with schizophrenia. Schizophrenia Research 196: 39–44 [PubMed: 28988914]

Merritt K, McGuire PK, Egerton A, Investigators H-MiS, Aleman AA, et al. 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: 667–81 [PubMed: 33881460]

Mollon J, Mathias SR, Knowles EEM, Rodrigue A, Koenis MMG, et al. 2020. Cognitive impairment from early to middle adulthood in patients with affective and nonaffective psychotic disorders. Psychological Medicine 50: 48–57 [PubMed: 30606277]

Murray RM, Lewis SW. 1987. Is schizophrenia a neurodevelopmental disorder? British Medical Journal (Clinical Research Education) 295: 681–82

Nestor PG, Forte M, Ohtani T, Levitt JJ, Newell DT, et al. 2020. Faulty executive attention and memory interactions in schizophrenia: prefrontal gray matter volume and neuropsychological impairment. Clinical EEG and Neuroscience 51: 267–74 [PubMed: 31608658]

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. Schizophrenia Bulletin 44: 1362–72 [PubMed: 29373755]

Patkee PA, Baburamani AA, 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: Clinical 25: 102139 [PubMed: 31887718]

Perkins DO, Gu H, Boteva K, Lieberman JA. 2005. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: A critical review and meta analysis. American Journal of Psychiatry 162: 1785–804 [PubMed: 16199825]

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: 185–95 [PubMed: 25017496]

Pries L-K, Dal Ferro GA, 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. Epidemiology and Psychiatric Sciences 29: e182 [PubMed: 33200977]

Purohit DP, Perl DP, Haroutunian V, Powchick P, Davidson M, Davis KL. 1998. Alzheimer disease and related neurodegenerative diseses in elderly patients with schizophrenia: a postmortem neuropathologic study of 100 cases. Archives of General Psychiatry 55: 205–11 [PubMed: 9510214]

Radhakrishan R, Skosnik PD, Ranganathan M, Naganawa M, Toyonaga T, et al. 2021. In vivo evidence of lower synaptic vescile density in schizophrenia. Molecular Psychiatry

Rajji TK, Voineskos AN, Butters MA, Miranda D, Arenovich T, et al. 2013. Cognitive performance of individuals with schizophrenia across seven decades: a study using the MATRICS Consensus Cognitive Battery. American Journal of Geriatric Psychiatry 21: 108–18

Ranganathan M, Bromet EJ, Eaton WW, Pato C, Schwartz JE. 1992. The natural course of schizophrenia: a review of first-admission studies. Schizophrenia Bulletin 18: 185–207 [PubMed: 1621068]

Reichenberg A, Harvey PD. 2007. Neuropsychological impairments in schizophrenia: integration of performance-based and brain imaging findings. Psychological Bulletin 133: 833–58 [PubMed: 17723032]

Ribe AR, Larsen TM, 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: 1095–101 [PubMed: 26444987]

Roalf DR, Ruparel K, Verma R, Elliott MA, Gur RE, Gur RC. 2013. White matter organization and neurocognitive perfomance variability in schizophrenia. Schizophrenia Research 143: 172–78 [PubMed: 23148898]

Rodrigue AL, Knowles EEM, Mollon J, Mathias SR, Koenis MMG, et al. 2019. Evidence for genetic correlation between human cerebral white matter microstructure and inflammation. Human Brain Mapping 40: 4180–91 [PubMed: 31187567]

Roussos P, Haroutunian V. 2014. Schizophrenia: susceptibility genes and oligodendroglial and myelin related abnormalities. Frontiers in Cellular Neuroscience 8

Rund BR. 1998. A review of longitudinal studies of cognitive functions in schizophrenia patients. Schizophrenia Bulletin 24: 425–35 [PubMed: 9718634]

Rund BR. 2009. Is schizophrenia a neurodegenerative disorder? Nordic Journal of Psychiatry 63: 196–201 [PubMed: 19235629]

Salthouse TA. 2009. When does age-related cognitive decline begin? Neurobiology of Aging 30: 507–14 [PubMed: 19231028]

Salthouse TA. 2019. Trajectories of normal cognitive aging. Psychology and Aging 34: 17–24 [PubMed: 30211596]

Seidman LJ, Cherkerzian S, Goldstein JM, Agnew-Blais J, Tsuang MT, Buka SL. 2013. Neuropsychological performance and family history in children at age 7 who develop adult schizophrenia or biploar psychosis in the New England Family Studies. Psychological Medicine 43: 119–31 [PubMed: 22575089]

Selemon LD, Goldman-Rakic PS. 1999. The reduced neuropil hypothesis: a circuit based model of schizophrenia. Biological Psychiatry 45: 17–25 [PubMed: 9894571]

Sexton CE, Walhovd KB, Storsve AB, Tamnes CK, Westlye LT, et al. 2014. Accelerated changes in white matter microstructure during aging: A longitudinal diffusion tensor imaging study. Journal of Neuroscience 34: 15425–36 [PubMed: 25392509]

Shah JN, Qureshi SU, Jawaid A, Schulz PE. 2012. Is there evidence for late cognitive decline in chronic schizophrenia? . Psychiatric Quarterly 83: 127–44 [PubMed: 21863346]

Sheffield JM, Karcher NR, Barch DM. 2018. Cognitive deficits in psychotic disorders: a lifespan perspective. Neuropsychology Review 28: 509–33 [PubMed: 30343458]

Sheitman B, Lieberman JA. 1998. The natural history and pathophysiology of treatment resistant schizophrenia. Journal of Psychiatric Research 32: 143–50 [PubMed: 9793867]

Sibille E 2013. Molecular aging of the brain, neuroplasticity, and vulnerability to depression and other brain-related disorders. Dialogues in Clinical Neuroscience 15: 53–65 [PubMed: 23576889]

Smucny J, Dienel SJ, Lewis DA, Carter CS. 2021. Mechanisms underlying dorsolateral prefrontal cortex contributions to cognitive dysfunction in schizophrenia. Neuropharmacology

Southard EE. 1915. On the topographical distribution of cortex lesions and anomalies in dementia praecox, with some account of their functional significance. American Journal of Insanity 71: 603–71

Stone WS, Cai B, Liu X, Grivel MM, 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 JAMA Psychiatry 77: 1–11

Stone WS, Keshavan MS. 2012. Medical co-morbidity in schizophrenia In The Neuropsychology of Schizophrenia, ed. Marcopulos B, Giuliano AJ, pp. 159–80

Stone WS, Mesholam-Gately RI, Giuliano AJ, Woodberry KA, Addington J, et al. 2016. Healthy adolescent performance on the MATRICS Cognitive Consensu Battery (MCCB): Developmental data from two samples of healthy volunteers. Schizophrenia Research 172: 106–13 [PubMed: 26896388]

Stone WS, Roe AH, Tsuang MT. 2007. Overlapping of the spectra: physical comorbidity between schizophrenia and affective disorders In The Overlap of Affective and Schizophrenic Spectra, ed. Marneros A, Akiskal AH, pp. 207–23. Cambridge: Cambridge University Press

Stone WS, Seidman LJ. 2016. Neuropsychological and structural imaging endophenotypes in schizophrenia In Developmental Psychopathology, ed. Cicchetti D, pp. 931–65. Hoboken, New Jersey: John Wiley & Sons, Inc.

Stroup TS, Olfson M, Huang C, Wall MM, Goldberg T, et al. 2021. Age-specific prevalence and incidence of dementia diagnoses among older US adults with schizophrenia. JAMA Psychiatry 78

Szoke A, Trandafir A, Dupont ME, Meary A, Schurhoff F, Leboyer M. 2008. Longitudinal studies of cognition in schizophrenia:meta-analysis. British Journal of Psychiatry 192: 248–57

Takahashi N, Sakurai T, Davis KL, Buxbaum JD. 2011. Linking oligodendrocyte and myelin dysfunction to neurocircuitry abnormalitiesin schizophrenia. Progress in Neurobiology 93: 13–24 [PubMed: 20950668]

Takeuchi H, Siu C, Remington G, Fervaha G, Zipursky RB, et al. 2019. Does relapse contribute to treatment resistance? Antipsychotic response in first- vs. second-episode schizophrenia. Neuropsychopharmacology 44: 1036–42 [PubMed: 30514883]

Teeuw J, Ori APS, Brouwer RM, de Zwarte SMC, Schnack HG, et al. 2021. Accelerated aging in the brain, epigenetic aging in blood, and polygenic risk for schizophrenia. Schizophrenia Research 231: 189–97 [PubMed: 33882370]

Tsuang MT, Stone WS, Faraone SV. 2000. Towards reformulating the diagnosis of schizophrenia. American Journal of Psychiatry 147: 1041–50

Tsuang MT, Woolson RF, Fleming JA. 1979. Long-term outcome of major psychoses. I. Schizophrenia and affective disorders compared with psychiatrically symptom-free surgical conditions. Archives of General Psychiatry 36: 1295–301 [PubMed: 496548]

Waber DP, De Moor C, Forbes PW, Almli CR, Botteron KN, 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. Journal of the International Neuropsychological Society 13: 729–46 [PubMed: 17511896]

Wang J, Kochunov P, Sampath H, Hatch KS, Ryan MC, et al. 2021. White matter brain aging in relationship to schizophrenia and its cognitive deficit. Schizophrenia Research 230: 9–16 [PubMed: 33667860]

Weinberger DR. 1987. Implications of normal brain development for the pathogenesis of schizophrenia. Archives of General Psychiatry 44: 660–69 [PubMed: 3606332]

Weinberger DR, McClure RK. 2002. Neurotoxicity, neuroplasticity, and magnetic imaging morphology. Archives of General Psychiatry 59: 553–58 [PubMed: 12044198]

Wijtenburg SA, Wright SN, Korenic SA, Gaston FE, Ndubuizu N. 2017. Altered glutamate and regional cerebral blood flow levels in schizophrenia: a (1)H-MRS and pCASL study. Neuropharmacology 42: 562–71

Yokomizo JE. 2020. SuperAgers in low-education setting: how to assess cognition. International Psychogeriatrics 32: 165–67 [PubMed: 32122415]

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. American Journal of Psychiatry 176: 811–19 [PubMed: 31256609]

Zanelli J, Mollon J, Sandin S, Reichenberg A. 2020a. Are visual memory deficits in recent-onset psychosis degenerative? Response to Smucny et al. American Journal of Psychiatry 177: 356–57 [PubMed: 32233688]

Zanelli J, Mollon J, Sandin S, Reichenberg A. 2020b. Further analysis of cognitive change in schizophrenia and other psychoses in the decade following the first episode: response to Panayiotou et alet al. American Journal of Psychiatry 177: 354–55

Zilkens RR, Bruce DG, Duke J, Spilsbury K, Semmens JB. 2014. Severe psychiatric disorders in mid-life and risk of dementia in late-life(age 65-84 years: a population based case-control study. Current Alzheimer Research 11: 681–93 [PubMed: 25115541]

Zipursky RB, Menezes NM, Streiner DL. 2014. Risk of symptom recurrence with medication discontinuation in first-episode psychosis: a systematic review. Schizophrenia Research 152: 408–14 [PubMed: 23972821]

Zipursky RB, Reilly TJ, Murray RM. 2013. The myth of schizophrenia as a progressive brain disease. Schizophrenia Bulletin 39: 1363–72 [PubMed: 23172002]

Zornberg G, Tsuang MT. 1999. Elmer E. Southard, M.D. 1876-1920. American Journal of Psychiatry 156: 1263