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Accelerated aging in schizophrenia and related disorders: Future research

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ABSTRACT

Several lines of evidence suggest schizophrenia is a segmental progeria, that is, some but not all aspects of accelerated aging may be present. However, the evidence has not been consistent. Problems with matching and confounding may account for some of these discrepancies. Given the etiopathophysiological heterogeneity of schizophrenia, it is possible that only a specific pathophysiological group within schizophrenia is associated with progeroid features, while others are not, or that one group is associated with a particular segment of aging features, while other progeroid features are found in another pathophysiological subgroup. In the aging research field, significant progress has been made in identifying the molecular pathways that confer aging: epigenetic changes, inflammation, proteostasis, adult stem cell function, metabolic changes, and adaptation to stress, and macromolecular damage. In addition to replication and clarification of existing kinds of evidence, examining these aging pathways would improve our understanding of progeria in schizophrenia.

1. Introduction

Nearly everyone contemplates aging at some point. People worry about getting older because they will get sick and lose their ability to enjoy life and contribute to the world around them. The notion that aging begets disease seems obvious and yet it is only in recent years that a consensus has emerged recognizing aging as the biggest risk factor for a wide range of chronic diseases, including Alzheimer's, a range of degenerative neurologic conditions, metabolic and cardiovascular syndromes and most forms of adult-onset cancer, to name just a few.

Aging is a "progressive deterioration of physiological function, an intrinsic age-related process of loss of viability and increase in vulnerability" (Comfort, 1964). Medawar (1952) defined aging as "a collection of changes that render human beings more likely to die." This quote derives from Medawar's famous book, *An Unsolved Problem in Biology*, a title that in 1952 was certainly true. While the work of Medawar and many others has provided plausible evolutionary theories of aging (Kirkwood, 2005), a mechanistic understanding of the physiologic changes driving pathology during aging has only recently begun to coalesce. A recent review from a diverse collection of scientists in the aging field defined seven processes that collectively influence aging (Kennedy et al., 2014). While these processes can be defined in different ways (Lopez-Otin et al., 2013), there is for the first time a strong sense in the aging field that clear themes are emerging.

A class of diseases termed progeroid disorders exhibit segmental aging, that is, some but not all features of aging appear to be accelerated. Hutchinson-Gilford and Werner syndrome are two classic examples, and debate has continued for decades as to whether the causes of these diseases are overlapping with those of normal aging. Another theme has also emerged: that classical non-aging diseases may either be associated with segmental aging or may accelerate aging. In other words, disease may beget aging which in turn begets disease. For instance, Down's syndrome patients have early onset Alzheimer's disease, as well as a range of other age-related conditions (Malt et al., 2013). Chronic viral infection, notably cytomegalovirus, may be an example of a disease that drives aspects of aging, in this case accelerating senescence in the immune system (Frasca and Blomberg, 2016). These findings suggest that we are just beginning to understand the relationship between aging and disease.

2. Schizophrenia and aging

In 1968, two psychiatrists wrote, "There is a rather common notion among psychiatrists that patients with schizophrenia appear younger than their chronological age" (Gottheil and Joseph, 1968). When the authors tested this hypothesis they found the opposite, that people with schizophrenia were judged to look older than control subjects. To our

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knowledge, this is the first article that could be considered to suggest schizophrenia was associated with accelerated aging. Nearly thirty years later, DeLisi (1997) suggested that schizophrenia was a "lifetime disorder of brain plasticity, growth, and aging." She focused on abnormal aging in the brain and did not suggest this abnormality extended to the rest of the body. When we suggested schizophrenia was a syndrome of accelerated aging, we cited studies of brain structure and function, but also pointed out findings raising the possibility that abnormal aging occurs in the periphery as well (Kirkpatrick et al., 2008).

If schizophrenia is a syndrome of accelerated aging, it may be a segmental progeroid syndrome, that is, only some aspects of accelerated aging may be present. This possibility complicates interpretation of evidence on the hypothesis of accelerated aging in schizophrenia and related disorders, as a failure to find a specific aspect of normal aging would not refute the hypothesis.

We describe below an approach to determine whether schizophrenia indeed resembles segmental aging and, if so, which aging pathways are affected. As the purpose of this article is to suggest directions for more definitive hypothesis testing, we do not present a thorough review of the literature.

3. Research strategy

In our 2008 article (Kirkpatrick et al., 2008) we discussed evidence related to mortality patterns, cognitive decline, diabetes, and pulse pressure, as well as risk factors shared by schizophrenia and aging-related disorders such as diabetes. We also cited a single imaging study that found an increased rate of brain volume loss in people with schizophrenia compared to control subjects (Ho et al., 2007). We suggested further tests of the hypothesis could include studies of other physiological measures known to change with normal aging, including insulin resistance, blood lipid concentrations, pulse pressure, bone density, clouding of the eye lens, thinning and wrinkling of the skin, thinning of the hair, and muscle mass. Since that time, our meta-analyses of studies of antipsychotic-naïve patients have found abnormal glucose tolerance and insulin resistance, as well as elevated prolactin concentrations in both men and women (Greenhalgh et al., 2017; González-Blanco et al., 2016). However, studies of aging and cognition have had mixed results (e.g., Harvey, 2014; Irani et al., 2011; Rodriguez-Jimenez et al., 2015). Other measures linked to aging have also been examined, including telomere length, pulse pressure, levels of androgens in males, and prostaglandin concentrations (Fernandez-Egea et al., 2011; Lee et al., 2016). Findings of increased inflammation (Miller et al., 2011) and oxidative stress (Finkel and Holbrook, 2000; Miller et al., 2014) are also consistent with the hypothesis of accelerated aging. Contradictory findings have been published on some of these measures, for instance on telomere length (Fernandez-Egea et al., 2009a,b; Jeste et al., 2016). There is a relative lack of longitudinal studies of the accelerated aging hypothesis, but such studies would be helpful in testing associations found using a cross-sectional design.

There are many possible causes of contradictory results in this area. To conduct stronger tests of the accelerated aging hypothesis, it will be important to consider confounding by antipsychotic medications. Most antipsychotics in current use are associated with weight gain, with concomitant increases in inflammation and glucose intolerance. Glucose intolerance and inflammation are both aging-related conditions and may induce other aging-related changes. As a consequence, without comparison groups with similar exposure to antipsychotics, findings on age-related variables are vulnerable to confounding, leaving the field with ambiguous interpretations of the evidence. Several findings consistent with accelerated aging, with medium to large effect sizes, have been found in antipsychotic-naïve patients (Fernandez-Egea et al., 2009a,b, 2011), and study of this population is an important strategy for the study of aging.

A number of other factors can also influence metabolic and physiological measures associated with aging and so confound associations with age-related phenomena. These include the familiar variables of age, ethnicity, and gender. However, to use the example of glucose tolerance, several other variables are also known to be important: alcohol, smoking, diet, cortisol, and body mass index or waist-hip ratio. Matching on socioeconomic status of family of origin is also desirable as this should minimize possible confounding by factors such as childhood nutrition, lifetime diet, and exposure to environmental toxins. To our knowledge, only one study of an aging-related variable in people with nonaffective psychosis either dealt with these factors through matching or choice of patient population, or examined their relationship to the outcome variable, in this case glucose tolerance (Fernandez-Egea et al., 2009a; Kirkpatrick et al., 2012).

Another difficulty in testing the accelerated aging hypothesis is that schizophrenia is itself a heterogeneous disorder. It is possible that a specific etiopathophysiological group or groups within schizophrenia is associated with progeroid features, while others are not, or that one group is associated with a particular segment of aging features, while other progeroid features are found in another pathophysiological subgroup. For instance, preliminary evidence suggests that deficit and nondeficit groups, that is, those with and without primary, enduring negative symptoms, may differ on two aging-related measures, inflammation and glucose tolerance (Garcia-Rizo et al., 2012a,b; Kirkpatrick et al., 2009). Replication is needed for these findings, but they illustrate the kind of complexity that may be encountered.

There a number of strategies other than the deficit/nondeficit categorization that may prove to be useful in defining pathophysiological subgroups. Examples include a comparison between patients with and without a specific environmental or genetic risk factor (Malaspina et al., 2015), differing trajectories of cognitive impairment (Thompson et al., 2013), or differences in biomarkers such as (state or trait) inflammation (Miller et al., 2011; Kirkpatrick and Miller, 2013). Level of function, or a variation of level of function such as community living vs. institutionalization, seems less promising as there are many paths to poor functional status. For instance, deficit patients have poor function compared to patients without primary, enduring negative symptoms, but severe and treatment-nonresponsive positive symptoms can also cause poor function. Combining such groups in a study of poor function/good function groups may weaken any signal-to-noise ratio.

4. Aging: mechanisms and pathways

The breadth of evidence on accelerated aging, which includes epidemiological studies, physiological challenges, and imaging, is intriguing but to date it largely consists of studies of aging-related variables that do not bring us much closer to an understanding of any mechanism(s) of accelerated aging. Studies that test for the presence of abnormalities in the relevant mechanistic pathways would be desirable.

In the aging research field, significant progress has been made in identifying the molecular pathways that confer aging. A recent review listed seven areas of biology that are implicated in aging (Kennedy et al., 2014), and other reviews have come to similar conclusions (Lopez-Otin et al., 2013). These areas are understood at differing levels of mechanistic depth; however, they serve as a good framework for discussing the known links between schizophrenia and aging and for designing future studies. Each of the seven is briefly discussed below.

It should be noted that these pathways have a surprising level of inter-connectedness. Disruption of any one pathway during aging can easily lead to dysfunction in others. Therefore, while aging may have several drivers, the process can be considered as a network. Initial changes during aging drive other changes, leading to a progressive loss of homeostasis. In a segmental progeria, where dysfunction in only a subset of pathways of aging is observed, perturbations of the network may have more unpredictable outcomes.

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