Journal of Psychiatric Research 85 (2017) 42–48

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Leukocyte telomere length: Effects of schizophrenia, age, and gender

Owen M. Wolkowitz [a, 1], Dilip V. Jeste [b, c, d, *, 1], Averria Sirkin Martin [b, d], Jue Lin [a], Rebecca E. Daly [b, d], Chase Reuter [b, d], Helena Kraemer [e]

[a] University of California San Francisco School of Medicine (UCSF), San Francisco, CA, USA
[b] Department of Psychiatry, University of California, San Diego, La Jolla, CA, 92093, USA
[c] Department of Neurosciences, University of California, San Diego, La Jolla, CA, 92093, USA
[d] Sam and Rose Stein Institute for Research on Aging, University of California, San Diego, La Jolla, 92093-0738, USA
[e] Stanford University School of Medicine, Stanford, CA, USA

ARTICLE INFO

Article history:
Received 26 August 2016
Received in revised form
28 September 2016
Accepted 3 October 2016

Keywords:
Schizophrenia
Telomere
Aging
Gender
Antipsychotics
Life style

ABSTRACT

Background: Schizophrenia is linked with early medical comorbidity and mortality. These observations indicate possible "accelerated biological aging" in schizophrenia, although prior findings are mixed, and few such studies have examined the role of gender. One putative marker of biological aging is leukocyte telomere length (LTL), which typically shortens with age.

Methods: We assessed LTL in phenotypically well characterized 134 individuals with schizophrenia (60 women and 74 men) and 123 healthy comparison subjects (HCs) (66 women and 57 men), aged 26 to 65 years.

Results: Overall, LTL was inversely associated with age ($t(249) = -6.2$, $p < 0.001$), and a gender effect on the rate of LTL decrease with age was found ($t(249) = 2.20$, $p = 0.029$), with men declining more rapidly than women. No significant overall effect of diagnosis on the rate of decline was detected. However, at the average sample age (48 years), there was a significant gender effect in both schizophrenia and HC groups ($t(249) = 2.48$, $p = 0.014$), with women having longer LTL than men, and a significant gender X diagnosis effect ($t(249) = 2.43$, $p = 0.016$) - at the average sample age, women with schizophrenia had shorter LTL than HC women.

Discussion: Gender, not the diagnosis of schizophrenia, was the major factor involved with LTL shortening across the age range studied. We discuss the constraints of a cross-sectional design and other methodological issues, and indicate future directions. Understanding the impact of schizophrenia on biological aging will require separate evaluations in men and women.

Published by Elsevier Ltd.

1. Introduction

Schizophrenia is associated with major medical co-morbidity, a 3- to 5-fold increase in premature death, and an estimated 15–20 years of shortened life span (Dickerson et al., 2014; Kilbourne et al., 2009; Kirkpatrick et al., 2008; Olfson et al., 2015). This has led to a suggestion that schizophrenia is associated with accelerated biological aging (Anthes, 2014; Dawes et al., 2011; Kirkpatrick et al., 2008; Kochunov et al., 2013; Koutsouleris et al., 2014; Lindqvist et al., 2015; Okusaga, 2014; Schnack et al., 2016; Shivakumar et al., 2014). Whereas men have overall higher death rates than women, mortality ratios in schizophrenia (standardized to the general population with respect to age, race/ethnicity and geographic region) are higher in women than in men with schizophrenia, with cardiovascular disease being a leading cause of premature death in both genders (Olfson et al., 2015). The causes of medical co-morbidity and premature mortality in schizophrenia are not fully understood but are likely multifactorial, including lifestyle factors (Chwastiak et al., 2011; Robson and Gray, 2007), antipsychotic drugs, and poor access to health care (McCabe and Leas, 2008) as well as intrinsic biological differences (Ringen et al., 2014). Reasons for possible gender-related differences in mortality ratios in schizophrenia remain obscure.

Whereas chronological age is measured in calendar years, biological age is defined physiologically and is often more closely associated with disease processes (Cawthon et al., 2003; Epel,

* Corresponding author. Stein Institute for Research on Aging, University of California–San Diego, 9500 Gilman Drive, #0664, La Jolla, CA, 92093-0738, USA.
E-mail address: djeste@ucsd.edu (D.V. Jeste).
[1] Co-first authors.

http://dx.doi.org/10.1016/j.jpsychires.2016.10.015
0022-3956/Published by Elsevier Ltd.

2009; Lindqvist et al., 2015). Accelerated biological aging occurs when biological age outpaces chronological age (Lindqvist et al., 2015). One marker of biological age is telomere length (TL), often measured in leukocytes (LTL), since it progressively declines with age and may be inversely related to diseases of aging and mortality (Bojesen, 2013; Cawthon et al., 2003; Mather et al., 2011; Muezzinler et al., 2013; Svensson et al., 2014). However, peak LTL (shortly after birth), the age at which a decline begins, the rate of decline, and when death interrupts the process, vary among individuals (Svensson et al., 2014), suggesting important inter-individual differences in the rates of biological aging (Epel, 2012; Lindqvist et al., 2015; Muezzinler et al., 2013). Variability in telomere length among people of the same chronological age raises the possibility that telomere shortening is potentially modifiable (Bojesen, 2013).

Telomeres are DNA–protein complexes that cap chromosomal DNA ends, protecting chromosomes from damage. When telomeres reach a critically short length, cells undergo replicative senescence or apoptosis or can become genomically unstable (Blackburn, 2005). Telomere length is influenced by genetic factors (Broer et al., 2013), demographic factors and environmental exposure. Telomeres shorten with advancing age (Muezzinler et al., 2013) and are generally shorter in men than in women (Gardner et al., 2014). Telomeres also shorten with repeated mitosis in somatic cells, with replication- and nuclease-associated telomeric DNA damage, and with exposure to oxidative stress, certain cytotoxins, inflammation, and possibly stress hormones (Effros, 2011; Epel et al., 2004; Lindqvist et al., 2015; von Zglinicki, 2002; Wolkowitz et al., 2011). Among the most important lifestyle- and experience-related factors that may impinge on LTL are stress (Epel, 2009; Epel et al., 2004), tobacco use (Babizhayev et al., 2011), exercise (Puterman et al., 2010); and diet (Epel, 2009; Freitas-Simoes et al., 2016), as well certain medical risk factors, such as visceral adiposity (Epel, 2009) (but see (Diaz et al., 2010)), metabolic stress (Epel, 2009) and certain chronic viral infections (e.g., cytomegalovirus) (Effros, 2011). It is unknown if these genetic, lifestyle, and environmental factors also affect LTL in schizophrenia, or if they differ between women and men with schizophrenia.

The published literature on LTL in schizophrenia is based on cross-sectional studies. Because concomitants of aging, including changes in LTL with age, are processes taking place within individuals over time, with individual differences in time course, longitudinal studies are ultimately necessary to fully understand these phenomena. However, if the changes over time are generally monotonic (e.g., LTL decreasing within individuals over time), results shown to be age-related in cross-sectional studies are likely to be even more strongly age-related in longitudinal studies, as cross-sectional studies tend to attenuate time effects. Consequently, cross-sectional studies provide clues as to which factors may be considered in the design of such studies. Thus far, cross-sectional studies have reported mixed results. Several investigations found shorter LTL in persons with schizophrenia than in healthy comparison subjects (HCs) (Fernandez-Egea et al., 2009; Kao et al., 2008) or at least in subgroups of individuals with more chronic, severely psychotic, or treatment-resistant illness (Kota et al., 2015; Li et al., 2015; Rao et al., 2016; Yu et al., 2008) (but see (Lin, 2015)), possibly suggesting accelerated biological aging (Jeste et al., 2011; Kirkpatrick et al., 2008). However, one large study reported longer LTL in schizophrenia than in HCs (Nieratschker et al., 2013). Yet other studies have detected no difference in LTL between individuals with schizophrenia and HCs (Li et al., 2015; Malaspina et al., 2014; Mansour et al., 2011). Reasons for discrepancies in findings among these studies are not known, but may include inadequate sample sizes, differing gender distributions, quality of diagnostic evaluations, nature of the comparison sample, chronicity and severity of illness, medical illnesses, medication history, and history of treatment responsiveness, along with demographic and lifestyle factors such as age, diet, body-mass index (BMI), exercise, and tobacco use. Nonetheless, reviews and meta-analyses of these studies of LTL (Darrow et al., 2016; Lindqvist et al., 2015) support decreased LTL in schizophrenia compared to HCs, with an effect size of approximately d = 0.34, with the effect size being larger in subgroups of subjects who were either drug-naïve (d = 0.56) or poor responders to medication (d = 0.97) (Darrow et al., 2016; Lin, 2015; Polho et al., 2015).

The present study, using a relatively large sample size with adequate representation of women and men with schizophrenia and HCs, well matched in age from 26 to 65 years (mean age = 48), was designed to assess the simultaneous association of age, gender, and diagnosis with LTL. We hypothesized that shorter LTL would be associated with older age (Muezzinler et al., 2013), male gender (Gardner et al., 2014) and diagnosis of schizophrenia (Darrow et al., 2016; Lindqvist et al., 2015). Demographics as well as certain factors associated with schizophrenia or aging, such as cigarette consumption, physical exercise, nutrition, stress, psychiatric ratings, antipsychotic medication doses, and physical health, were also explored.

2. Methods

2.1. Study participants

This report is based on an analysis of baseline data from an ongoing longitudinal study of biological aging in schizophrenia (NIH R01 MH094151-01 [PI: Dilip V. Jeste]). Although we previously published data on high sensitivity C-reactive protein (hs-CRP) (Joseph et al., 2015), F2-isoprostanes (Lee et al., 2016), as well as cytokines (tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interferon-γ (IFN-γ) (Lee et al., In Press) and chemokines (Hong et al., In Press) in earlier subsets of this sample, the current report represents our first examination of LTL and its associations with demographic, psychiatric, and medical factors. The analyses were restricted to all participants who had LTL data available. These included 134 outpatients with either schizophrenia (N = 80, comprised of 61% women) or schizoaffective disorder (N = 54, comprised of 48% women), and 123 HCs (comprised of 48% women) with no history of major neuropsychiatric illness. All the subjects were recruited from the greater San Diego community and interviewed using the Structured Clinical Interview for the DSM-IV-TR (SCID) (Almeida and Xiao, 2007). Subjects were excluded if they had 1) other current DSM-IV-TR Axis I diagnoses; 2) alcohol or other substance (other than tobacco) abuse or dependence within 3 months prior to enrollment; 3) diagnosis of dementia, mental retardation, or a major neurological disorder; 4) or any medical disability that interfered with their ability to complete the study assessments. Most (91%) of the schizophrenia patients were receiving antipsychotic medication at the time of their assessment. The study protocol was reviewed and approved by the UC San Diego Human Research Protections Program (Project #101631). All study subjects provided written informed consent to participate.

2.2. Blood collection

Fasting blood samples were collected by trained nurses at the UC San Diego Clinical and Translational Research Institute (CTRI) lab. Whole blood was collected for telomere assays in 8.5 mL lavender top plastic EDTA tubes on ice. Samples were stored in a −80° freezer until transportation to UC San Francisco for assay in the Blackburn Lab.