Schizophrenia Research xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

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

Letter to the Editor

# Telomere length and early trauma in schizophrenia☆

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ARTICLE INFO

*Article history:*
Received 11 November 2017
Received in revised form 25 February 2018
Accepted 26 February 2018
Available online xxxx

*Keywords:*
Early trauma
Schizophrenia
Childhood trauma
Leukocytes
Telomeres
Stress

ABSTRACT

*Background:* Childhood trauma is emerging as a risk factor for schizophrenia, but its mechanism with respect to etiology is unknown. One possible pathway is through leucocyte telomere length (LTL) shortening, a measure of cellular aging associated with trauma. This study examined early trauma and LTL shortening in schizophrenia and considered sex effects.
*Methods:* The early trauma inventory (ETI) was administered to 48 adults with DSM-5 schizophrenia and 18 comparison participants. LTL was measured using qPCR.
*Outcomes:* Cases had significantly more global trauma ($F = 4.10$, $p < 0.01$) and traumatic events ($F = 11.23$, $p < 0.001$), but case and control groups had similar LTL ($1.91 \pm 0.74$ and $1.83 \pm 0.62$: $p = 0.68$). The association of early trauma and LTL differed by sex in cases and controls (Fisher's R: $Z < 0.05$). Significant negative associations were shown in male cases and, conversely, in female controls. For example, physical punishment was associated LTL shortening in males' cases ($r = -0.429$, $p < 01$). Only female controls showed significant telomere shortening in association with early trauma.
*Interpretation:* This data confirms the substantial excess of early trauma among schizophrenia cases. There were significant sex-differences in the relationship of the trauma to LTL, with only male cases showing the expected shortening. There were converse sex effects in the control group. Mean LTL was notably similar in cases and controls, despite the trauma-related shortening in male cases, cigarette smoking, older age and chronic illness of the cases. Factors may lengthen LTL in some schizophrenia cases. The converse sex differences in the cases are consistent with findings defective sexual differentiation in schizophrenia, consistent with other findings in the field.


## 1. Introduction

Early trauma exposure is a major risk factor for schizophrenia (Heins et al., 2011; Ruby et al., 2014; Varese et al., 2012), which is furthermore associated with clinical features in the disease, particularly with treatment refractory psychotic symptoms, including auditory hallucinations and command hallucinations (Carr et al., 2013; Heins et al., 2011; Rajkumar, 2015; Read et al., 2005; Ruby et al., 2017; Van Os et al., 2008; Varese et al., 2012). There are a number of possible pathways that could explain the relationship of early trauma to the development of schizophrenia (Read et al., 2001; Ruby et al., 2014; Veras et al., 2018) but none are yet shown to explain the association. One possible mechanism is the shortening telomere lengths by trauma. Shorter telomeres are a biological marker of cellular aging that has been linked to early trauma exposure in population studies (Epel et al., 2004; Kananen et al., 2010; Price et al., 2013; Shalev, 2012; Shalev et al., 2013).

Briefly, telomeres are tandem repeats of TTAGGG at both ends of mammalian chromosomes that form a protective cap to buffer genes against damage during replication. Telomere lengths decrease with each cell replication in somatic cells. Shorter telomeres predict fewer future cell divisions and more rapid cell senescence, ultimately triggering programmed cell death (apoptosis). Telomere length, usually measured

☆ Study was funded by NIMH Challenge Grant RC1MH088843.
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[1] Published posthumously by coauthors Mary Perrin and Raymond R. Goetz.

https://doi.org/10.1016/j.schres.2018.02.059
0920-9964/

as leukocyte telomere length (LTL) predicts lifespan as well as cellular aging (Armanios, 2013). Cortisol and dysregulated Hypothalamic Pituitary Axis (HPA) activity can reduce LTL, with shorter telomeres demonstrated in stressed women caring for partners with dementia and in numerous other comparable circumstances (Damjanovic et al., 2007; Oliveira et al., 2016). The enzyme telomerase, which normally lengthens telomeres in stem cells but is silenced in somatic cells, undergoes reduced activity from cortisol exposure in cultured T lymphocyte (Choi et al., 2008). Stress and elevated cortisol levels are furthermore linked to inflammation and oxidative stress, which also produce telomere erosion (Shalev, 2012). Glucocorticoids augment the oxidative stress that can produce double-stranded telomeric breaks leading to LTL shortening (Epel et al., 2004).Together these findings support a role for the HPA stress axis in telomere length maintenance.

Demonstrating that early trauma contributes to telomere shortening in schizophrenia may shed light on the contradictory findings concerning LTL in schizophrenia. An initial study reported shortened LTL in schizophrenia cases compared to controls, which was in keeping with the earlier mortality, cigarette smoking, cardiovascular diseases and chronic poor health of most persons with schizophrenia (Kao et al., 2008). For example, cigarette smoking is associated with shortened LTL in large population studies and the vast majority of cases, upwards of 80%, smoke cigarettes (McGrath et al., 2007). Moreover, shortened telomeres were observed in several other psychiatric disorders (Darrow et al., 2016). However subsequent studies found no mean difference in LTL between cases and controls and yet other reports described longer LTL in groups of schizophrenia cases (Nieratschker et al., 2013; Rao et al., 2016).

This study tested the hypothesis that childhood trauma is related to shorter LTL in schizophrenia. If so, then childhood adversity may contribute to the disease through cellular aging. We used a reliable and valid structured interview to assess trauma exposure in a sample of exceptionally well-characterized schizophrenia cases and healthy controls.

## 2. Materials and method

The study was conducted at a large urban public hospital and was approved by the Institutional Review Boards of NYU Medical Center and Bellevue Hospital Center. All participants provided written informed consent. Cases with schizophrenia or schizoaffective disorder on stable medication doses were recruited from inpatient and outpatient treatment settings and healthy controls were recruited from local postings and internet- recruitment sites. Healthy control participants were excluded if they met criteria for an Axis I diagnosis in the last two years, had ever taken psychiatric medications, or had any personal or family history of psychosis in first-degree relatives on structured interviews.

To determine DSM diagnosis, Master's level clinicians conducted assessments with the Diagnostic Interview for Genetic Studies (DIGS) and utilized hospital records (Nurnberger et al., 1994). Childhood trauma exposure was assessed with the early trauma inventory (ETI) (Bremner et al., 2000), which includes measures of general traumatic events, physical abuse, emotional abuse, and sexual abuse before age 18, as well as general trauma after the age of 18. Analyses of inter-rater reliability, test-retest reliability, internal consistency, and convergent validity all indicate that the ETI is a reliable and valid assessment for the measurement of reported childhood trauma (Bremner et al., 2000). For all participants, cigarette smoking history was categorized as never, past, or current. Lifetime cumulative antipsychotic equivalents were not assessed, but cases were categorized based on their current psychiatric medications: those taking any Lithium, clozapine, Risperdal, aripiprazole, haloperidol injection, other atypical agents, none and unknown.

For LTL, DNA was extracted from lymphocytes (EAG Laboratories; Hercules, CA, USA) by quantitative polymerase chain reaction (qPCR) with iCycler real-time PCR system and several modifications, as we have previously detailed (Cawthon, 2002; Malaspina et al., 2014). Each sample was assayed in triplicate with the Rotor-Gene SYBR Green PCR Master Mix from Qiagen. LTL was determined by calculating the telomere to single copy gene ratio (T/S ratio) using ΔCt. The T/S ratio of each sample (x) was normalized relative to the mean T/S ratio of the reference sample [$2 - (\Delta ctx - \Delta Ctr) = 2 - \Delta\Delta Ct$], which was used to construct standard curves for a reference and a validation sample.

## 3. Data analysis

Data was entered and verified using the SIR Database Management Software (SIR 2002, SIR Pty Ltd) and IBM/SPSS Statistics 23 was used for the analyses. Descriptive statistics and distributions of all measures were examined, whether continuous or categorical, to identify key features (e.g. non-normal distribution, outliers, skewness) that impacted inferential methods. Age, education, and LTL were compared across diagnosis and sex using ANOVA. Age of illness onset was compared across the male and female cases using the *t*-test statistic. The ETI Domains were analyzed using MANCOVA with age as a covariate. Smoking status was analyzed using the Chi-squared statistic. Due to the small sample size, spearman correlations were performed between LTL and the ETI Domains and scatterplots were run to assess for outliers. Male and female cases with outlier (elongated) LTL were determined statistically using the SPSS "Examine procedure," which identifies values that are not within the interquartile range of values; i.e. within 1.5 standard deviations from the median. Post-hoc analysis investigated paternal age of male outliers.

## 4. Results

Schizophrenia cases were older and less educated than controls, and only two controls were current or past smokers compared to 32 of 48 cases, demonstrating a substantial group effect for smoking status among the schizophrenia cases ($p < 0.001$). Schizophrenia cases had significantly greater exposure to trauma than controls, particularly for general trauma and emotional abuse, with no significant sex differences in their trauma exposures or LTL measurements. However, the mean LTL measurements were similar for the groups of cases and controls, respectively 1.91 (0.74) and 1.83 (0.62). There was no significant group level association between LTL and subjects age (Spearman's non-parametric statistics) in either the cases (rho = −0.009) or controls (rho = −0.203). In cases, LTL was also not significantly related to current medication groups, with sample sizes and mean LTL as follows: Lithium (n = 4), mean 1.57 (SD 0.12); clozapine (n = 6), 2.14 (0.67); Risperdal (n = 12), 1.95 (0.55); aripiprazole (n = 5), 2.32 (0.99); haloperidol injection (n = 1), 2.15; other atypical agents (n = 10), 1.74 (0.16); none (4), 1.92 (0.56) and unknown medications (6), 2.05 (0.53).

There were no significant associations between LTL and trauma indices for general events, physical punishment, emotional abuse, sexual events and the grand total of events (r's = −0.20 to +0.22) for cases or controls. Sex-specific analyses showed significant sex differences in the correlations of LTL with early trauma exposure. LTL was shorter in association with trauma severity in male cases, but not in female cases (−0.320 vs. 0.447: Fisher's R to Z Transformation < 0.05). The effect of trauma to shorten LTL with particularly strong for male cases exposed to early physical punishment and LTL ($r = -0.429$, $p < 01$). Conversely, female controls showed greater correlations between LTL reductions and trauma severity than male controls (−0.275 vs. 0.688: Fisher's R to Z Transformation < 0.05).

## 5. Discussion

This study demonstrated significantly greater exposure to early trauma for schizophrenia cases than healthy control subjects, supporting a large prior literature. While the trauma severity was not significantly

Please cite this article as: Riley, G., et al., Telomere length and early trauma in schizophrenia, Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.02.059