Journal of Affective Disorders 186 (2015) 241–248

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Review

Is bipolar disorder associated with accelerating aging? A meta-analysis of telomere length studies

Gabriela D. Colpo [a], Daniella D. Leffa [b], Cristiano A. Köhler [c], Flávio Kapczinski [d,e], João Quevedo [a,f], André F. Carvalho [g,*]

[a] Center for Translational Psychiatry, Department of Psychiatry and Behavioral Sciences, The University of Texas Medical School at Houston, Houston, TX, USA
[b] Laboratório de Neurociências, Programa de Pós-Graduação em Ciências da Saúde, Unidade Acadêmica de Ciências da Saúde, Universidade do Extremo Sul Catarinense, Laboratório de Biologia Celular e Molecular, Criciúma, SC, Brazil
[c] Memory Research Laboratory, Brain Institute, Federal University of Rio Grande do Norte (UFRN), Natal, Brazil
[d] Department of Psychiatry and Behavioral Sciences, The University of Texas Medical School at Houston, UT Center of Excellence on Mood Disorders, Houston, TX, USA
[e] Laboratory of Molecular Psychiatry, Centro de Pesquisas Experimentais, Hospital de Clínicas de Porto Alegre, and Instituto Nacional de Ciencia e Tecnologia for Translational Medicine, Porto Alegre, Rio Grande do Sul, Brazil
[f] Laboratório de Neurociências, Programa de Pós-Graduação em Ciências da Saúde, Unidade Acadêmica de Ciências da Saúde, Universidade do Extremo Sul Catarinense, Criciúma, SC, Brazil
[g] Translational Psychiatry Research Group and Department of Clinical Medicine, Faculty of Medicine, Federal University of Ceará, Fortaleza, CE, Brazil

ARTICLE INFO

Article history:
Received 22 April 2015
Received in revised form
18 June 2015
Accepted 20 June 2015
Available online 26 July 2015

Keywords:
Bipolar disorder
Meta-analysis
Telomere
Accelerated aging
Healthy controls
Cellular senescence

ABSTRACT

Background: Bipolar disorder (BD) is associated with a reduced life expectancy compared to the general population mainly due to a high prevalence of comorbid somatic illnesses. A model of accelerated aging has been proposed as a potential explanation to these epidemiological findings. Nevertheless, studies measuring telomere length (TL) in patients with BD compared to healthy controls have provided mixed results.

Objective: To compare TL between BD patients and healthy controls, and to search for potential modeP < rators for observed differences.

Methods: We performed a systematic review and meta-analysis of original studies comparing TL in patients with BD vs. healthy controls published up to February 24th, 2015 in main electronic databases. Heterogeneity was explored through meta-regression and subgroup analysis.

Results: Seven studies met inclusion criteria ($N=1115$). There was no difference in TL between participants with BD and healthy controls (Hedges's $g=-0.012$; 95% CI $=-0.418$ to 0.393, $P=0.952$). There was no evidence for publication bias. Heterogeneity was high ($I^2=89.65\%$). In meta-regression analyses, the percentage of females in healthy control samples ($P=0.04$) and the methodological quality of included studies ($P<0.001$) emerged as significant moderators, while subgroup analyses suggest that the type of assay employed to measure TL and age- and gender-matching of BD and HC participants may contribute to heterogeneity.

Conclusions: Telomere length does not differ between participants with BD vs. healthy controls; this finding does not support the view of BD as an illness associated with accelerated cellular aging. However, more studies controlling for potential confounders are necessary.

Contents

* Correspondence to: Department of Clinical Medicine, Faculty of Medicine, Federal University of Ceará, Rua Prof. Costa Mendes, 1608, 4° andar, 60430-040 Fortaleza, CE, Brazil. Fax: +55 85 33668054.
E-mail address: andrefc7@terra.com.br (A.F. Carvalho).

http://dx.doi.org/10.1016/j.jad.2015.06.034
0165-0327/

1. Introduction

Bipolar disorder (BD) is a chronic and severe mental disorder characterized by recurring episodes of (hypo) mania, depression, as well as mixed episodes (Phillips and Kupfer, 2013). The underlying patho-etiology of BD remains incompletely elucidated but may involve the complex interaction of genetic and environmental factors (Nurnberger et al., 2014; Uher, 2014). Furthermore, several lines of evidence indicate that a cascade of events, including but not limited to an over-activation of inflammatory pathways, along with oxidative and nitrosative stress (O&NS) and a diminished neurotrophic support lead to neuroprogressive changes (Anderson and Maes, 2015; Berk et al., 2011; Modabbernia et al., 2013; Scola and Andreazza, 2015).

The neuroprogressive nature of BD is supported by clinical observations that point to differences in the severity of clinical presentation and response to treatment in individuals in early vs. late stages of BD (Berk et al., 2011). Furthermore, staging models for BD have been proposed (Duffy, 2014; Vieta et al., 2011). In addition, emerging evidence indicates that individuals at later stages of BD may have more impaired cognitive and psychosocial functioning (Grande et al., 2014; Rosa et al., 2014).

More recently, BD has been conceptualized as an illness associated with accelerated aging processes (Rizzo et al., 2014; Simon et al., 2006; Sodhi et al., 2012). The starting point of this theory rests on phenomenological similarities between BD and aging, including but not limited to a decline in cognitive performance and functional status, a greater propensity to the development of age-related general medical conditions (e.g., obesity and cardiovascular diseases), as well as a reduced lifespan (Liu et al., 2013; Rizzo et al., 2014; Weiner et al., 2011). Thus, aging-related biomarkers may be of value to monitor illness progression in BD (please see Rizzo et al. (2014) for a review).

Telomeres are specialized structures located at the end of chromosomes, which consist of DNA tandem repeats of $(TTAGGG/CCCTAA)_n$ as well as stabilizing proteins, such as telomeric repeat-binding factors and TRF1-interacting nuclear factor 2 (Aubert and Lansdorp, 2008; Hug and Lingner, 2006; Wysoczanska, 2013). Since telomerase levels are limited in the living cell, after each cell division telomeres shorten due to the "end of replication problem". Thus, telomere erosion is a relevant biochemical marker of cellular senescence (Shalev et al., 2013).

Evidence points to shortened telomeres in peripheral blood cells of individuals with BD compared to healthy controls (Lima et al., 2014; Rizzo et al., 2013), whereas other studies did not find shortened telomeres in BD compared to healthy volunteers (Mansour et al., 2011). Similarly, telomere lengths did not differ in the cerebellar gray matter of individuals with BD compared to controls (Zhang et al., 2010). Prompted by these discrepant findings, herein we performed a systematic review and meta-analysis of studies measuring telomere length (TL) in samples with a diagnosis of BD vs. healthy controls (HCs). A second aim of this study was to investigate potential moderators of the difference in telomere length between subjects with BD and healthy volunteers.

2. Materials and methods

A systematic review and meta-analysis was performed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Cochrane group guideline recommendations (Higgins and Green, 2013; Moher et al., 2009). The process includes literature review, eligibility criteria of the retrieved references, assessment of the methodological quality of included studies, extraction of outcomes and relevant variables and meta-analysis of the data.

2.1. Search strategy

We searched the Pubmed/MEDLINE, EMBASE, PsycInfo and Web of Sciences databases from inception through February 24th, 2015 (see Supplementary online material for search strings used in each database search). This search strategy was augmented through hand-searching of reference lists of included articles and through tracking the citations of eligible references in Google Scholar.

2.2. Eligibility criteria

We included original human studies that reported data on telomere length in participants meeting Diagnostic and Statistical Manual for Mental Disorders (DSM) and/or International Classification of Diseases (ICD) diagnostic criteria for bipolar disorder (American Psychiatric Association, 2013; World Health