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Telomere length and telomerase in a well-characterized sample of individuals with major depressive disorder compared to controls

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Summary
Background: Leukocyte telomere length (LTL) is a marker of cellular turnover and oxidative stress. Studies suggest major depressive disorder (MDD) is associated with oxidative stress, but examinations of MDD and LTL have yielded mixed results, likely because of differences in measurement methods and unmeasured confounding. This study examined LTL and telomerase activity in 166 individuals with MDD compared to 166 age- and gender-matched matched controls free of any psychiatric disorder, using well-validated assays and clinical assessment methods, and controlling for a range of potential confounders.

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Methods: Subjects aged 18 to 70 were evaluated by trained raters and provided blood for LTL and telomerase activity measurement. LTL was assayed using Southern blot and replicated with qPCR, and telomerase activity was assayed with a repeat amplification protocol using a commercial kit.
Results: There was no significant difference in telomere length for individuals with MDD [mean (SD) = 9.1 (3.0) kbp] compared to controls [mean(SD) = 8.9(2.5) kbp] measured by Southern blot ($p = 0.65$) or by confirmatory qPCR ($p = 0.91$) assays. Controlling for potential confounders did not alter the results. Telomerase activity did not differ by MDD diagnosis overall ($p = 0.40$), but the effect of MDD was significantly modified by gender ($t(299) = 2.67$, $p = 0.0079$) even after controlling for potential confounders, with telomerase activity significantly greater only in males with MDD versus controls.
Conclusion: Our well-characterized, well-powered examination of concurrently assessed telomere length and telomerase activity in individuals with clinically significant, chronic MDD and matched controls failed to provide strong evidence of an association of MDD with shorter LTL, while telomerase activity was lower in men with MDD.

1. Introduction

Major depressive disorder (MDD) has been repeatedly associated with increased risk for medical morbidity (Evans et al., 2005) and mortality (Everson-Rose et al., 2004; Gump et al., 2005). This association has been found to remain true after accounting for potential health behavior confounds, such as smoking and lower levels of exercise (Penninx et al., 1998). Growing data suggest that this increased risk may be explained by an increased rate of age-related diseases such as cardiovascular disease (e.g. Wassertheil-Smoller et al., 2004) or cancer (e.g. Pinquart and Duberstein, 2010). Specifically, increasing evidence suggests that the elevated risk for age-related disease in MDD may be due in part to an abnormal stress and immune response (e.g. Chrousos, 1998; Pariante and Miller, 2001; Raison and Miller, 2003; Simon et al., 2006), which may accelerate biological aging through chronic wear on cells and tissue, increasing vulnerability to age-related disease (Kop et al., 2010; Maes et al., 2011). Leukocyte telomere length (LTL) has recently emerged as an index of cellular aging. Telomeres are nucleoprotein complexes consisting of long arrays of double stranded TTAGGG repeats associated with telomeric repeat-binding proteins and found at the ends of linear chromosomes. It is thought that telomeres function to 'cap' chromosomal termini and prevent end-to-end recombination, thereby counteracting or delaying shortening during cell division by maintaining chromosomal integrity (Blackburn, 2010).

Telomerase is an enzyme that adds DNA sequence repeats (''TTAGGG'') to the 3′ end of DNA strands in the telomere regions. Telomerase levels are usually insufficient to maintain telomere length in somatic cells, and progressive attrition occurs with each cell division, resulting in metered loss of telomeres that may serve as a cellular mitotic clock ultimately limiting the number of cell divisions and cellular life span. Further, while evidence suggests telomere length is in part genetically determined, increased cellular turnover in the presence of stress-related oxidative damage may exacerbate accelerated telomere shortening, suggesting that telomere-driven replicative senescence may be primarily a stress response (Lung et al., 2007; Vasa-Nicotera et al., 2005; von Zglinicki et al., 2005).

Leukocyte telomeres have been proposed to be an ideal marker of chronic stress-accelerated aging due to MDD because they serve as a marker of cellular turnover, oxidative stress, and telomerase regulation. To date, a number of studies have investigated the relationship between LTL and MDD using a variety of assays to measure telomere length [e.g. quantitative polymerase chain reaction (qPCR), Southern blot, and flourescent in situ hybridiziation (FISH)], assessing MDD with a range of measures (e.g. structured clinical interviews vs. self-report questionnaires), and differentially controlling for potential confounding variables (for review see Schutte and Malouff, 2015). Results have been mixed particularly with adjustment for the presence of concurrent medical morbidity. Multiple cross-sectional investigations have provided evidence that a history of MDD or current MDD is associated with shorter telomere length in comparison to controls (Garcia-Rizo et al., 2013; Hartmann et al., 2010; Karabatsiakis et al., 2014; Lung et al., 2007; Simon et al., 2006; Wikgren et al., 2012) including in an investigation that controlled for age, sex, education, body mass index (BMI), smoking, alcohol use, physical activity, and somatic diseases (Verhoeven et al., 2013). Further, in a recent meta-analysis using data from 25 studies (including the studies referenced here), Schutte and Malouff (2015) found a small association between depression and shorter LTL ($r = -0.12$, $p < 0.001$).

However, many studies report mixed results including Hoen et al. (2011) who found significantly shorter LTL in MDD compared to controls after controlling for age and sex, but the findings were only trending significance after controlling for BMI, smoking, diabetes, left ventricular ejection fraction, statin use, antidepressant use, physical inactivity, and anxiety [MDD: 0.85(0.02) vs. no MDD 0.89(0.01) T/S ratio, $p = 0.06$]. Other investigations found no overall association between LTL and MDD but significant association with subpopulations with greater cumulative depression exposure (Wolkowitz et al., 2011) or on antidepressants (Needham et al., 2015). Additionally, Shalev et al. (2014) reported significant acceleration of telomere length erosion from age 26 to 38 in males with major depression, but not females. Other cross-sectional studies have failed to demonstrate any significant association between LTL and