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Leukocyte telomere length predicts SSRI response in major depressive disorder: A preliminary report

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Abstract

Short leukocyte telomere length (LTL) may be associated with several psychiatric disorders, including major depressive disorder (MDD). Short LTL has previously been associated with poor response to psychiatric medications in bipolar disorder and schizophrenia, but no studies have prospectively assessed the relationship of LTL to SSRI response in MDD. We assessed pre-treatment LTL, depression severity (using the Hamilton Depression Rating Scale [HDRS]), and self-reported positive and negative affect in 27 healthy, unmedicated adults with MDD. Subjects then underwent open-label treatment with a selective serotonin reuptake inhibitor (SSRI) antidepressant for eight weeks, after which clinical ratings were repeated. Analyses were corrected for age, sex and BMI. “Non-responders” to treatment (HDRS improvement <50%) had significantly shorter pre-treatment LTL, compared to “Responders” ($p=0.037$). Further, shorter pre-treatment LTL was associated with less improvement in negative affect ($p<0.010$) but not with changes in positive affect ($p=0.356$). This preliminary study is the first to assess the relationship between LTL and SSRI response in MDD and among the first to prospectively assess its relationship to treatment outcome in any psychiatric illness. Our data suggest that short LTL may serve as a vulnerability index of poorer response to SSRI treatment, but this needs examination in larger samples.

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The remaining authors report no disclosures.

Keywords

Affect; Affective disorder; Antidepressants; Biomarker; Depression; Major depression; Mood disorders; Selective serotonin reuptake inhibitors; Telomer; Treatment response

1. INTRODUCTION

Major depressive disorder (MDD) is a severe and disabling disorder [1] that is recognized by the World Health Organization (WHO) as the leading cause of disability, affecting an estimated 350 million people worldwide. Although the molecular and cellular mechanisms underlying MDD are not fully known, changes in cellular aging, indexed by shortened leukocyte telomeres, may be a novel aspect of MDD pathophysiology [2, 3].

Telomeres are specialized DNA nucleoprotein complexes that, along with bound protective proteins, cap the chromosomal ends of DNA, serving to protect the chromosomes from damage and to promote genomic stability and integrity [4]. When somatic cells divide, telomeres may not be fully replicated due to the “end-replication problem” [4]. Further, cumulative exposure to certain cytotoxic environments, such as oxidative stress and inflammation, may lead to telomere shortening [4]. Consequently, average human telomere length (TL) (often assessed in leukocytes [as LTL] or peripheral blood mononuclear cells [PBMCs]) generally shortens with age unless acted upon by telomerase, the major telomere-lengthening enzyme, or by alternative telomere lengthening mechanisms [4, 5]. When telomeres become critically shortened, the genome may become unstable and/or the cell may undergo senescence, causing activation of cellular mechanisms that promote dysfunction and disease, such as inflammation, mitochondrial damage, proliferation failure, and cell death [2, 4].

Recent studies have investigated TL in relation to numerous psychiatric disorders [2, unpublished], and several studies have shown shortened TL in MDD [6–13], although exceptions exist [14–16]. Shortened LTL in MDD and other psychiatric disorders could have pathophysiological significance by indicating accelerated aging at the cellular level and by synergizing with depression diagnosis in predicting mortality in certain populations [17]. However, few studies have investigated the association between LTL and psychopharmacological outcomes. To date, only three studies (one in bipolar disorder and two in schizophrenia) have examined the relationship between LTL and treatment response to psychiatric medications [18–20], two of which assessed clinical treatment outcomes retrospectively [18, 19]. Martinsson et al. [18] retrospectively assessed lithium response in 121 patients with bipolar disorder and found that lithium non-responders had significantly shorter LTL than responders. Yu et al. [19] retrospectively assessed clinical response to antipsychotics in a group of 68 inpatients with schizophrenia, and found that poorer treatment response was associated with shorter LTL. Li et al. [20] assessed telomere length in 89 first-episode, antipsychotic-naïve patients with schizophrenia prior to beginning eight weeks of open-label risperidone treatment, and found that poorer treatment response (<50% symptom improvement after treatment) had shorter LTL. Additionally, a placebo-controlled study by Rasgon et al. [21] examined LTL as a predictor of antidepressant response to the

addition of Pioglitazone (a peroxisome proliferator-activated receptor [PPAR-γ] agonist) in 42 patients with unremitted MDD who were already attempting to treat their depression with another medication(s). This study found that patients with shorter LTL showed poorer response to the addition of Pioglitazone to their medication therapy and this relationship was not seen in the placebo group. However, no study has yet assessed the relationship between pre-treatment LTL and clinical response to a traditional antidepressant medication in MDD. Based on these prior studies, we hypothesized that shorter pre-treatment LTL would be associated with poorer observer-rated response to antidepressant medication in MDD. Secondary outcomes included self-reported changes in negative and positive affect.

2. METHODS

2.1. Subjects

Twenty-eight unmedicated adults (20–65 years of age) with current MDD were enrolled in an eight-week longitudinal study of SSRI treatment. Telomerase and LTL data of 13 of these subjects were reported previously [22, 23], however, none of these subjects had data previously presented on the relationship between LTL and treatment response. One of the 28 enrolled subjects was excluded due to the detection of periodontitis (an exclusionary criterion) during the course of antidepressant treatment, leaving 27 completing subjects. Subjects were recruited by flyers, bulletin board notices, Craigslist postings, newspaper ads, and clinical referrals. The Committee on Human Research of the University of California, San Francisco (UCSF) approved the study protocol. All study participants gave written informed consent to participate in this study and were compensated for participating, in addition to receiving free antidepressant treatment.

All subjects were diagnosed with MDD, without psychotic features, according to the Structured Clinical Interview for DSM IV-TR Axis I Disorders (SCID) [24] with a current 17-item Hamilton Depression Rating Scale (HDRS) [25] rating of ≥ 17. SCID diagnoses were confirmed by clinical interview with a Board-Certified psychiatrist. Subjects were excluded for presence of the following: bipolar disorder, psychotic symptoms during their current major depressive episode, history of psychosis outside of a mood disorder episode, any eating disorder or post-traumatic stress disorder (PTSD) within one month of entering the study, and substance abuse or dependence (including alcohol) within six months of entering the study. Co-morbid anxiety disorders (except PTSD) were allowed if MDD was considered the primary diagnosis. Study participants had no acute illnesses or infections, chronic inflammatory disorders, neurological disorders, or any other major medical conditions considered to be potentially confounding (e.g. cancer, HIV, diabetes, history of cardiovascular disease or stroke, etc.), as assessed by history, physical examinations and routine blood screening. All subjects were free of psychotropic medications (including antidepressants), hormone supplements, steroid-containing birth control or other potentially interfering medications, and had not had any vaccinations, for at least six weeks prior to enrollment in the study, and none were taking vitamin supplements above the U.S. recommended daily allowances (e.g., 90 mg/day for Vitamin C). Short-acting sedative-hypnotics were allowed as needed up to a maximum of three times per week, but none within one week prior to participation. Prior to each study visit, all subjects had to pass a

urine toxicology screen for drugs of abuse (marijuana, cocaine, amphetamines, phencyclidine, opiates, methamphetamine, tricyclic antidepressants, and barbiturates) and a urine test for pregnancy in women of child-bearing age.

2.2. Procedures

Subjects were admitted as outpatients to the UCSF Clinical and Translational Science Institute between the hours of 0800 and 1100, having fasted (except water) since 2200 hours the night before. Subjects were instructed to sit quietly and relax for 25 – 45 minutes before blood samples were obtained for LTL assessment and routine clinical labs to determine health. The severity of depressive symptoms was then rated using the HDRS [25] and positive and negative affect over the past seven days were rated using the Positive and Negative Affect Schedule (PANAS) [26]. PANAS data were only available for 20 of the subjects due to incomplete self-ratings from seven subjects.

To account for other variables that could affect telomere length and/or treatment response, we also assessed the following: (i) subjective stress using the Perceived Stress Scale (PSS) [27], (ii) level of physical activity using the “Vigorous Activity” section of the Yale Physical Activity Scale (YPAS) [28], and (iii) estimated lifetime depression chronicity using life history charting methods described by Post, et al. [29]. Clinical ratings and history-taking were performed blind to telomere length.

Following this baseline visit, subjects completed eight weeks of open-label outpatient treatment with an SSRI antidepressant, as determined to be clinically appropriate by the study psychiatrist. The decision regarding the specific SSRI prescribed was made based on clinical grounds such as medical history, family history, and potential side effects. To limit the range of treatments the choice of medication was limited to SSRI. The prescriber was blind to telomere length. Outpatient compliance with the medication regimen, as well as clinical evaluations and assessments of drug tolerability, were assessed by a telephone check-in at the end of Week 1 and an in-person check-in at the end of Week 4 and Week 8, at which time pill counts were performed. Thirteen of the subjects additionally had plasma antidepressant concentrations assessed at Week 4 and Week 8; in each of these subjects, plasma antidepressant concentrations were in the reported clinical range for that antidepressant, suggesting excellent compliance. Twenty subjects were treated with sertraline, two with fluoxetine, two with citalopram, and three with escitalopram. Medication dosages increased over the course of treatment as tolerated and as warranted by clinical response. Sertraline dosing began with 25 mg per day and increased to a maximum of 200 mg per day; fluoxetine and citalopram dosing began with 10 mg per day and increased to a maximum of 40 mg per day; escitalopram dosing began with 10 mg per day and increased to a maximum of 20 mg per day. See Table 1 for further information regarding SSRI dosing. At the end of the eight weeks of SSRI treatment, subjects were again rated with the HDRS and PANAS. Subjects with percentage improvement of < 50% on the HDRS following treatment were defined as “Non-responders” and those with percentage improvement of ≥ 50% were defined as “Responders,” [30].

2.3. Telomere Length Measurement

High molecular weight DNA was extracted from frozen whole blood (obtained at baseline) using commercially available reagents (Puregene, Gentra Systems, Qiagen, Valencia, CA). DNA quality and quantity were assessed with a nanodrop spectrophotometer and random samples were also assessed by agarose gel electrophoresis. The telomere length measurement assay was adapted from the published original method [31]. Briefly, the T (telomeric) and S (single copy gene) values of each sample were determined by quantitative polymerase chain reaction (PCR) using the following primers: *tel1b* [5′-CGGTTT(GTTTGG)5GTT-3′] and *tel2b* [5′-GGCTTG(CCTTAC)5CCT-3′] for T and *hbg1* [5′ GCTTCTGACACAACTGTGTTCACTAGC-3′] and *hbg2* [5′-CACCAACTTCATCCACGTTCACC-3′] for S (human beta-globin). Genomic DNA from HeLa cells was used as the reference to quantify the T and S values relative to the reference DNA sample by the standard curve method. All PCRs were carried out on a Roche Lightcycler 480 real-time PCR machine with 384-tube capacity (Roche Diagnostics Corporation, Indianapolis, IN). The telomere thermal cycling profile consisted of: cycling for T (telomeric) PCR: denature at 96°C for 1 minute; denature at 96°C for 1 second, anneal/extend at 54°C for 60 seconds, with fluorescence data collection, 30 cycles; cycling for S (single copy gene) PCR: denature at 96°C for one minute; denature at 95°C for 15 seconds, anneal at 58°C for one second, extend at 72°C for 20 seconds, eight cycles; followed by denature at 96°C for one second, anneal at 58°C for one second, extend at 72°C for 20 seconds, hold at 83°C for five seconds with data collection, 35 cycles. To control for inter-assay variability, eight control DNA samples were included in each run. In each batch, the T/S ratio of each control DNA was divided by the average T/S for the same DNA from 10 runs to obtain a normalizing factor. This was done for all eight control samples and the average normalizing factor for all 8 samples was used to correct the participant DNA samples to obtain the final T/S ratio. The T/S ratio for each sample was measured twice. If the duplicate T/S value and the initial value varied by more than 7%, the sample was run a third time and the average of the two closest values was reported. Using this method, the inter-assay coefficient of variation (CV) for telomere length measurement was 4%. Details of this method can be found in [32]. For presentation of the data, T/S ratios were converted to base pairs (bp) by the formula: bp = 3,274+ 2,413*(T/S). Telomere length assays were performed in two separate batches (13 samples in the first batch [9 Responders; 4 Nonresponders] and 14 samples in the second batch [6 Responders; 8 Non-responders]). As noted below, batch was entered as a covariate in all analyses. Lab personnel who performed the assay were blind to demographic and clinical data.

2.4. Statistical Analyses

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) v.22 (IBM Corp., Armonk, NY). All tests were 2-tailed with an alpha = 0.05. P-values between 0.05 and 0.10 are reported as trends. Comparisons of demographic and clinical characteristics between-groups (Responders vs. Non-responders) were performed using Mann-Whitney U and Chi-Square tests, with the exception of lifetime depression chronicity (in months), which was compared using analysis of covariance (ANCOVA) to correct for age. All data of interest were normally distributed. Age, sex, and body mass index (BMI) were defined a priori as covariates, due to their reported impact on LTL;

therefore, all analyses were corrected for age, sex, and BMI. Additionally, as LTL was analysed in two separate assay batches, all analyses were also corrected for assay batch. To evaluate the impact of other potential confounds, bivariate correlations were assessed between ethnicity, BMI, current tobacco use, current alcohol use, level of physical activity, household income, years of education, subjective stress, lifetime depression chronicity, and the measures investigated in this study (LTL, HDRS, and PANAS); no significant associations were found.

To examine our hypothesis that pre-treatment LTL predicts clinical response to SSRI treatment, we assessed whether "Non-responders" to treatment had significantly different pre-treatment LTL compared to "Responders," using ANCOVA, including age, sex, BMI, and LTL assay batch as covariates. To further explore the relationship between LTL and clinical response to SSRI treatment, Pearson correlations were performed to examine associations between pre-treatment LTL and the absolute change in HDRS depression severity ratings and the absolute change in PANAS total negative and positive affect ratings (Week 8 minus Baseline). Correlations were performed using residual values corrected for age, sex, BMI, and LTL assay batch. Confidence intervals for Pearson's correlation coefficients were calculated using Fisher's z transform.

3. RESULTS

3.1. Demographics and clinical response

Demographic and clinical characteristics of the sample are summarized in Table 1. As expected, HDRS and PANAS ratings significantly improved over the eight-week course of open-label SSRI treatment. Absolute HDRS ratings declined from 19.63 ± 3.32 to 9.78 ± 4.58 ($p<0.001$), representing a mean decrease of 49.2%. Clinical "response" was defined a priori as reduction in HDRS rating by 50% or greater [30]. By this definition, 15 participants (55.6%) were "Responders" and 12 (44.4%) were "Non-responders." Absolute PANAS negative affect ratings declined from 41.75 ± 9.58 to 27.75 ± 5.20 ($p<0.001$), representing a mean decrease of 30.6%. Absolute PANAS positive affect ratings increased from 26.85 ± 5.03 to 37.85 ± 10.44 ($p<0.001$), representing a mean increase of 43.6%.

When comparing the demographics and clinical characteristics of Responders vs. Non-responders (see Table 1), we see that Non-responders were older ($p=0.024$) and had higher BMI ($p=0.012$) than Responders. There were no significant between-group differences in sex, ethnicity, education, socioeconomic status, physical activity level, SSRI dose, lifetime depression chronicity, or any baseline clinical measure examined (PSS, PANAS, or HDRS).

3.2. Pre-treatment telomere length and clinical response

"Non-responders" had significantly shorter pre-treatment LTL than "Responders" (means [adjusted for age, sex and BMI] = 5470.03 ± 354.18 bp, vs. 5801.62 ± 346.39 bp) ($F[1,21]=4.985$, $p=0.037$, 95% CI [−640.439, −22.477], $d=0.947$; Figure 1). The five lowest adjusted LTL values in the dataset belonged to Non-responders; these individuals were examined and were not found to be different from the rest of the sample in regards to age (range 20–58) or any other demographic or baseline clinical value, so they were not

influentially driving the results. Further, shorter pre-treatment LTL was associated with less absolute improvement in HDRS ratings at the trend level (r=−0.367, p=0.060, 95% CI [−0.655 to 0.016]; Figure 2).

Lastly, shorter pre-treatment LTL was associated with less improvement in PANAS negative affect (r=−0.562, p=0.010, 95% CI [−0.804, −0.158]; Figure 3), but not with changes in PANAS positive affect (r=0.218, p=0.356, 95% CI [−0.249, 0.602]).

4. DISCUSSION

To the best of our knowledge, this is the first study to assess the relationship between LTL and clinical response to traditional antidepressants in MDD and is among the first to prospectively assess the relationship between LTL and psychopharmacological treatment response in any disease (see also [20,21]). We found that pre-treatment LTL was shorter in depressed individuals who subsequently did not respond to SSRI treatment (≤ 50% improvement in depression ratings) compared to those who did respond; this difference was determined to represent a large effect, as indicated by Cohen's d. Consistent with these findings, we found a trend toward shorter pretreatment LTL predicting less decline in absolute depression severity ratings, as well as significantly predicting less improvement in negative, but not positive, affect (dimensions that are considered orthogonal to each other [33]). Regarding this latter finding, it is interesting to note that at least one previous study that examined positive and negative features separately [38], found that LTL was negatively associated with pessimism ratings, but not significantly correlated with optimism ratings in post-menopausal women. These findings do not appear to be related to ethnicity, current tobacco use, current alcohol use, level of physical activity, household income, years of education, subjective stress, lifetime depression chronicity, or differences in SSRI dosing, which were similar by group and were not related to baseline LTL. Although Nonresponders were significantly older and had significantly higher BMI than Responders, our findings were significant after statistically correcting for these factors.

Four previous studies (reviewed in the Introduction) have reported that shorter LTL is associated with worse psychiatric response to medications; i.e. lithium in bipolar disorder [18], antipsychotics in schizophrenia [19, 20], and the addition of a PPAR-γ agonist in unremitted MDD [21]. Our study differs from, and adds to, these previous findings in several ways. The present study (i) examined LTL and treatment response to a traditional antidepressant in MDD; (ii) used standardized ratings instruments and utilized a prospective, rather than retrospective assessment of treatment response (as did half of the previously mentioned studies), yielding a more accurate evaluation of treatment response; (iii) used a clinically relevant treatment intervention administered by a single physician, lessening extraneous factors that could affect treatment response; (iv) was performed on depressed individuals who were medication-free for more than six weeks prior to having LTL assessed and commencing treatment, allowing us to assess clinical response to the SSRI relative to an unmedicated state; (v) employed stringent inclusion and exclusion criteria, ruling out individuals with potentially confounding medications, illnesses, or comorbid conditions; and (vi) had demographic data available regarding BMI, level of physical activity, current

alcohol and tobacco use, socioeconomic status, subjective stress, and lifetime depression chronicity, allowing these to be statistically controlled for where appropriate.

Though specific pathways are not known, putative mechanisms by which LTL regulation may be associated with antidepressant outcomes can be postulated. Several peripherally assessed biological systems have been independently associated with both shorter LTL and worse clinical response to antidepressants, including higher levels of pro-inflammatory cytokines [22, 34–39], oxidative stress [40], and more early adverse life events [41, 42]. However, several of these findings are based on small samples and/or require replication. Though we did not specifically test these mechanisms in this study, it is possible that shorter LTL indexes peripheral biochemical conditions (e.g., greater oxidative stress or inflammation) or life histories (trauma exposures) that bode poorly for antidepressant response. In addition, certain mechanisms may more directly link short leukocyte telomeres with poorer antidepressant response. For example, senescent $CD8^+$ T cells with short telomeres ($CD8^+CD28^-$) hypersecrete pro-inflammatory cytokines [43], which might adversely affect antidepressant response [44]. However, since we did not assess T cell subpopulations in this study, and since we do not have cytokine data available, we cannot directly test this hypothesis. Thus, shorter LTL may be an indirect reflection of some other processes that correlate with poor antidepressant response (e.g. inflammation, oxidative stress), or it may have intrinsic predictive value, although this seems less likely. In a previous small-scale study, we reported that relatively high pre-treatment PBMC telomerase activity was associated with poorer response to sertraline [23]. The present finding that shorter leukocyte telomeres are also associated with poorer response to SSRIs may complement these findings, though any mechanistic linkage is speculative.

4.1. Limitations

Limitations of the present study include (i) the use of a relatively small sample (particularly for the PANAS variables); (ii) the assessment of mixed leukocytes, making it difficult to determine if telomere length in specific leukocyte subpopulations is more closely related to treatment response and whether LTL differences reflect TL differences on a “per cell” basis vs. a shift in circulating leukocyte subpopulations; (iii) the open-label nature of the antidepressant therapy, which can confound drug response with placebo response (though an open-label design more closely resembles clinical settings and was a common factor across all study participants); (iv) the assessment of antidepressant response after eight weeks of treatment, rather than additionally including longer duration time points; and (v) the study of only one class of antidepressant, the SSRIs.

5. CONCLUSION

Our data suggest that LTL may be a novel biomarker for predicting open-label SSRI treatment response, although these findings must be considered preliminary pending larger-scale replication. If these and other emerging data are replicated, the telomere system may emerge as a novel locus of interest for clinical psychopharmacology [2, 45].

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Dr. Jue Lin is a consultant to Telomere Diagnostics Inc., formerly Telome Health Inc., a diagnostics company related to telomere biology, and owns stock in the company. The company had no role in this research or in writing this paper.

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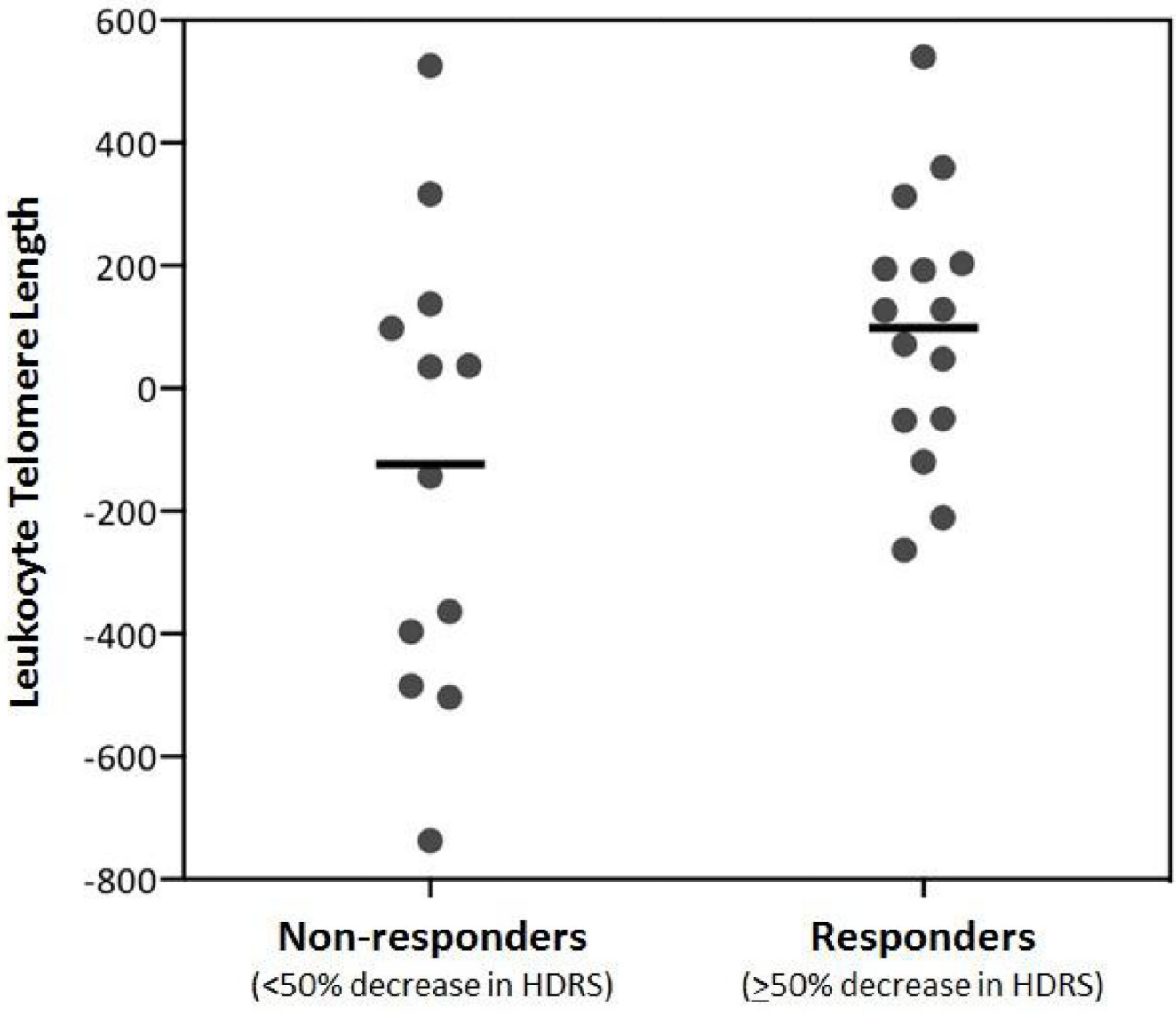

Figure 1.

Pre-treatment LTL in subjects classified as "Responders" (≥50% decrease in HDRS ratings over the eight weeks of treatment) and "Non-responders" (<50% decrease in HDRS ratings over the eight weeks of treatment ($F[1,21]=4.985$, $p=0.037$, 95% CI [−640.44, −22.74], $d=0.947$). Data represent residual values after adjusting for age, sex, BMI, and LTL assay batch; therefore, LTL data may be positive or negative.

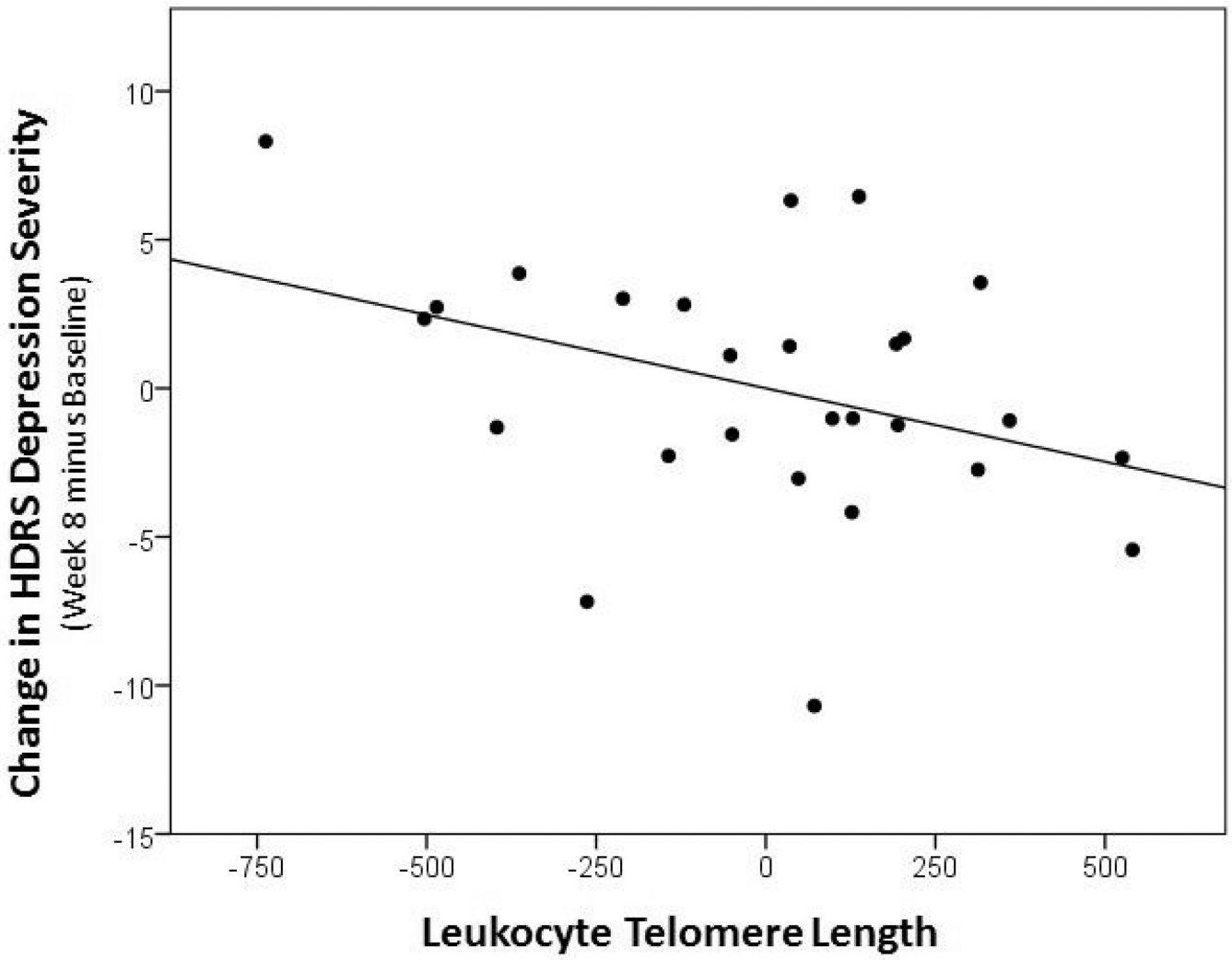

Figure 2.

Correlation between pre-treatment LTL and absolute change in HDRS Depression Severity over the eight weeks of treatment (Week 8 minus Baseline) (r=−0.367, p=0.060, 95% CI [−0.655 to 0.016]). Data represent residual values after adjusting for age, sex, BMI, and LTL assay batch; therefore, data may be positive or negative.

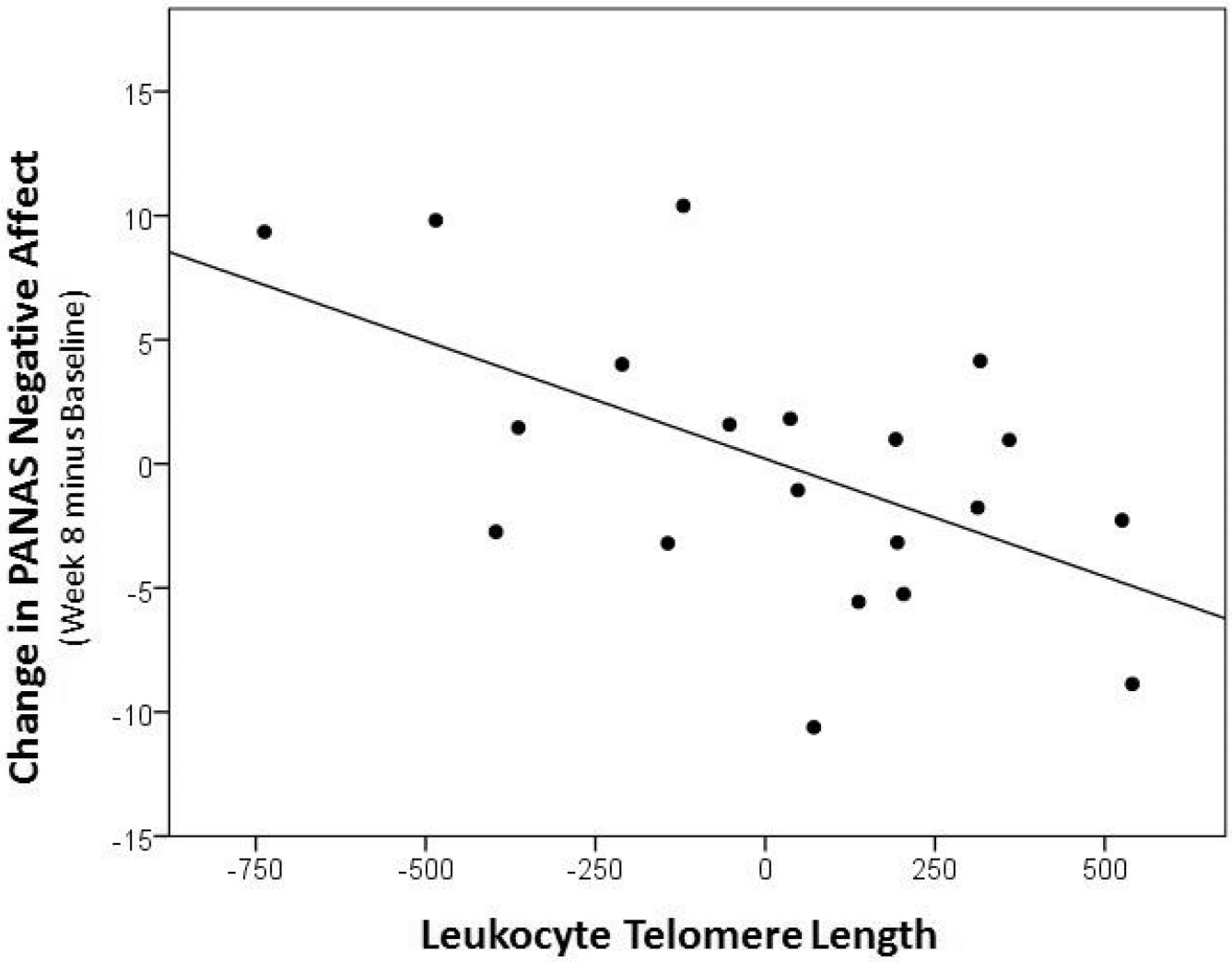

Figure 3.

Correlation between pre-treatment LTL and absolute change in PANAS Negative Affect over the eight weeks of treatment (Week 8 minus Baseline) (r=−0.562, p=0.010, 95% CI [−0.804, −0.158]). Data represent residual values after adjusting for age, sex, BMI, and LTL assay batch; therefore data may be positive or negative.

Table 1

Demographic and clinical characteristics of the sample.

	Total (n=27)	Non-responders (n=12)	Responders (n=15)	Non-responders vs. Responders
Age (years; mean ± SD)	37.56±11.73	43.33±13.23	32.93±8.14	U=44.0, p=0.024
Sex (males / females)	10 / 17	4 / 8	6 / 9	X^2=0.13, p=0.726
Ethnicity (Caucasian / non-Caucasian)	20 / 7	8 / 4	12 / 3	X^2=0.62, p=0.432
Years of education (mean ± SD)	16.15±1.98	16.00±2.56	16.27±1.44	U=83.0, p=0.724
Household Income[1] (mean ± SD)	$39,406±$26,169 (n=16)	$43,500±$31,035 (n=8)	$35,313±$21,589 (n=8)	U=58.5, p=0.643
BMI (kg/m^2; mean ± SD)	26.86±4.81	29.39±4.37	24.84±4.26	U=38.5, p=0.012*
Current Tobbacco Users (users / non-users; mean ± SD)	9 / 18	3 / 9	6 / 9	X^2=0.68, p=0.411
Alcohol Consumption[2] (# of drinks this month; mean ± SD)	15.65±3.33 (n=24)	20.38±5.34 (n=12)	10.92±3.73 (n=12)	U=50.0, p=0.199
HDRS pre-treatment (mean ± SD)	19.63±3.32	19.25±3.39	19.93±3.35	U=86.5, p=0.860
HDRS post-treatment (mean ± SD)	9.78±4.58	13.75±2.77	6.60±2.92	U=6.0, p<0.001*
PANAS Negative Scale pre-treatment[3] (mean ± SD)	41.75±9.58 (n=20)	41.44±9.57 (n=9)	42.00±10.05 (n=11)	U=49.0, p=0.970
PANAS Negative Scale post-treatment[3] (mean ± SD)	27.75±5.20 (n=20)	29.11±4.23 (n=9)	26.64±5.84 (n=11)	U=36.5, p=0.321
PANAS Positive Scale pre-treatment[3] (mean ± SD)	26.85±5.03 (n=20)	25.22±3.15 (n=9)	28.18±5.98 (n=11)	U=34.0, p=0.235
PANAS Positive Scale post-treatment[3] (mean ± SD)	37.85±10.44 (n=20)	33.00±5.20 (n=9)	41.82±12.13 (n=11)	U=33.5, p=0.223
YPAS Vigorous Activity Index Score[4] (mean ± SD)	259.08±336.21	374.22±427.37	166.96±214.39	U=64.5, p=0.207
Lifetime Depression Chronicity[5] (months; adjusted mean ± SD)	141.24±115.99	158.58±122.91	123.89±121.39	F=0.48, p=0.494
Baseline Subjective Stress[6] (mean ± SD)	24.61±6.19 (n=23)	26.20±5.67 (n=10)	23.38±6.51 (n=13)	U=47.5, p=0.276
Final SSRI Dose[7] (mg/day; mean ± SD)	99.07±34.31	112.50±34.86	88.33±32.55	U=52.0, p=.067

Abbreviations: BMI = Body Mass Index; HDRS = Hamilton Depression Rating Scale; PANAS = Positive and Negative Affect Schedule; YPAS = Yale Physical Activity Survey.

*Significant at the 0.05 level

[1]Household income reported by 16 participants (8 Responders; 8 Non-responders).

[2]Self-reported approximate number of drinks in the month prior to baseline blood draw; data available for 24 participants (12 Responders; 12 Non-responders).

[3]PANAS data only includes that from participants whom completed the scale at both pre- and post-treatment timepoints; data available for 20 participants (11 Responders; 9 Non-responders).

[4]YPAS Vigorous Activity Index Score is derived by multiplying the “frequency score” X the “duration score” X the participants’ weight (in kg); frequency scores range from 0–4 and duration scores range from 0–3 [28].

[5]Data is age-adjusted using Analysis of Covariance (ANCOVA); Lifetime depression chronicity was estimated using life history charting methods described by Post; only periods of time during which subjects met DSM-IV criteria for MDD were counted.

[6]Baseline subjective stress was measured using the Perceived Stress Scale (PSS) [27]; scores range from 0–40, in which higher scores indicate greater levels of perceived stress; data available for 23 participants (13 Responders, 10 Non-responders).

[7]Data for final SSRI dose is based on dose equivalency of Sertraline [46].