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# Insight meditation and telomere biology: The effects of intensive retreat and the moderating role of personality

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ABSTRACT

A growing body of evidence suggests that meditation training may have a range of salubrious effects, including improved telomere regulation. Telomeres and the enzyme telomerase interact with a variety of molecular components to regulate cell-cycle signaling cascades, and are implicated in pathways linking psychological stress to disease. We investigated the effects of intensive meditation practice on these biomarkers by measuring changes in telomere length (TL), telomerase activity (TA), and telomere-related gene (TRG) expression during a 1-month residential Insight meditation retreat. Multilevel analyses revealed an apparent TL increase in the retreat group, compared to a group of experienced meditators, similarly comprised in age and gender, who were not on retreat. Moreover, personality traits predicted changes in TL, such that retreat participants highest in neuroticism and lowest in agreeableness demonstrated the greatest increases in TL. Changes observed in TRGs further suggest retreat-related improvements in telomere maintenance, including increases in *Gar1* and *HnRNPA1*, which encode proteins that bind telomerase RNA and telomeric DNA. Although no group-level changes were observed in TA, retreat participants' TA levels at post-assessment were inversely related to several indices of retreat engagement and prior meditation experience. Neuroticism also predicted variation in TA across retreat. These findings suggest that meditation training in a retreat setting may have positive effects on telomere regulation, which are moderated by individual differences in personality and meditation experience. (ClinicalTrials.gov #NCT03056105).


## 1. Introduction

An emerging literature suggests that meditation practice and associated lifestyle interventions may promote healthy biological profiles, including alterations to stress-related physiological processes implicated in disease (Pace et al., 2009; Sudsuang et al., 1991; Turan et al., 2015). Among the biomarkers potentially affected by meditation practice are telomeres (Alda et al., 2016; Hoge et al., 2013), the related enzyme telomerase (Jacobs et al., 2011; Lavretsky et al., 2013; Lengacher et al., 2014), and the expression of telomere-related genes (Bhasin et al., 2013; Duraimani et al., 2015; Epel et al., 2016). Telomeres are nucleoprotein complexes at the ends of eukaryotic chromosomes that protect DNA from instability and degradation (Blackburn, 2000). Telomeres shorten incrementally during cell division and in response to cellular damage, making telomere length (TL) a valuable indicator of cellular aging and physiological stress (Blackburn, 2005, 1991;

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Harley et al., 1990). Longer telomeres are generally indicative of positive health outcomes (Blackburn et al., 2015; Lin et al., 2010; Puterman and Epel, 2012), whereas shorter telomeres are associated with, and in some cases causally linked to, a number of degenerative and age-related diseases, such as high blood pressure and cardiovascular disease (Blackburn et al., 2015; Codd et al., 2013; Lin et al., 2010; Puterman and Epel, 2012; Shalev et al., 2013; Zhan et al., 2017). Optimal TL is regulated and maintained by a complex network of molecular components collectively referred to as the telomere interactome (Robles-Espinoza et al., 2015; Zheng et al., 2014). A key component of this interactome is telomerase (TA), an enzyme that elongates telomeres by synthesizing telomeric DNA via the reverse transcriptase function of its enzymatic component, hTERT (or TERT), and its RNA template component, hTR (also referred to as TER or TERC; Blackburn, 2005; Zheng et al., 2014). Other proteins and molecular components of the interactome facilitate correct folding of telomerase cofactors, assembly of the telomerase holoenzyme (i.e., the biochemically active compound), intracellular trafficking of telomerase, and the replication, repair, and maintenance of telomeres, among other functions.

Both TL and TA are sensitive to a variety of psychosocial and behavioral influences (Blackburn et al., 2015; Puterman and Epel, 2012; Révész et al., 2016; Robles-Espinoza et al., 2015; Shalev et al., 2013), suggesting that links between psychological stress, health, and disease may be mediated, in part, by dynamic changes in telomere biology. For example, longer TL has been linked to higher levels of adaptive qualities such as conscientiousness (Edmonds et al., 2015), optimism and emotional intelligence (Schutte et al., 2016), whereas shorter TL has been associated with neuroticism (van Ockenburg et al., 2014), anxiety (Hoen et al., 2013), and lifetime incidence of major depressive disorder (Wolkowitz et al., 2011). Additionally, perceived and biological measures of stress (Epel, 2009; Epel et al., 2010, 2004; Shalev et al., 2013; Tomiyama et al., 2012) and recent life adversity (Révész et al., 2016) are associated with shorter TL, and individuals who experience prolonged reactivity to stressors exhibit shorter TL and lower TA (Puterman and Epel, 2012). Collectively, these findings suggest that psychosocial stressors and their biological consequences contribute to telomere erosion—but that adaptive or resilient psychological profiles might offer some protection against this degradation (Schutte et al., 2016).

Given the importance of telomere function in cellular health and longevity, interventions that mitigate telomere shortening—or promote telomere lengthening—may have profound health implications. Meditation training, which has long been theorized to improve psychological well-being (Ekman et al., 2005; Wallace and Shapiro, 2006) is one such promising approach. Broadly defined, meditation encompasses a variety of mental training techniques drawn from a number of cultures and contemplative traditions, which—depending on technique and tradition—are intended to cultivate an array of beneficial qualities, including stability of attention, relaxation, behavioral regulation, altruistic motivations, and spiritual development (Britton and Lindahl, 2017; Dahl et al., 2015; Lutz et al., 2015; Mehrmann and Karmacharya, 2013; Slagter et al., 2011).

Meditation retreats are designed to facilitate concentrated training in these techniques by allowing practitioners to engage in periods of full-time intensive practice, often in a secluded environment under the guidance of experienced teachers. Empirical evidence suggests that interventions incorporating Buddhist-derived meditation practices in both retreat and non-retreat contexts may reduce anxiety (Goyal et al., 2014; Platt et al., 2016; Sahdra et al., 2011) and depression (Epel et al., 2016) and influence psychological and physiological processes implicated in stress responding (Pace et al., 2009; Rosenkranz et al., 2013; Sudsuang et al., 1991), which may in turn affect telomere regulation. Moreover, a recent review of meditation retreats suggests that there may be added benefits to practicing in the retreat format (Khoury et al., 2015).

Ornish et al. (2008) were the first to investigate the link between meditation practice and TA, finding increased TA in prostate cancer patients following a 3-month comprehensive lifestyle intervention involving meditation. Our laboratory subsequently corroborated this link in a non-clinical sample engaged in a 3-month residential meditation retreat (Jacobs et al., 2011). Participants of this retreat practiced *shamatha* meditation techniques (Wallace, 2006), which emphasize the development of calm, focused attention and meditative quiescence. At the end of the intervention, retreat participants exhibited higher levels of TA in peripheral blood mononuclear cells (PBMCs) as compared to a wait-list control group matched on age, gender, and meditation experience. Importantly, retreat participants' post-intervention TA levels were mediated by increases in self-reported environmental mastery (i.e., perceived control) and purpose in life, as well as decreases in neuroticism—indicating a potential link between meditation-related changes in psychological factors and telomere regulation. Unfortunately, because TA was only measured at the end of retreat, this study was unable to rule out pre-existing group differences or to determine if TA increased over the course of the intervention (Jacobs et al., 2011). However, since these initial studies, additional research has substantiated the link between meditation and TA in both healthy adults (Epel et al., 2016; Rao et al., 2015; Tolahunase et al., 2017) and clinical populations (Daubenmier et al., 2012; Lavretsky et al., 2013; Lengacher et al., 2014; Ornish et al., 2013).

Much of the extant meditation literature has emphasized the assessment of TA because changes in TL were thought to take months or years, exceeding the typical duration of a meditation intervention. This view is changing, however, and researchers have begun to examine the effects of meditation practice on TL as well. An uncontrolled study found increased TA and a marginal increase in TL following a 12-week intervention involving yoga and meditation (Tolahunase et al., 2017). Additionally, two cross-sectional studies reported meditation practitioners having longer telomeres than meditation-naive comparison groups (Alda et al., 2016; Hoge et al., 2013—in women only). Only two studies have assessed longitudinal changes in TL with a controlled design, and these were in cancer patients undergoing 8-week Mindfulness Based Stress Reduction (MBSR) programs (Carlson et al., 2015; Lengacher et al., 2014). Neither of these studies showed changes in TL in the MBSR groups; however, one found TL declines in controls but maintenance in the intervention groups (Carlson et al., 2015), suggesting that meditation practice may nevertheless hold protective effects. The heterogeneity of these findings suggests that the target population and the duration and intensity of a given intervention may be important explanatory variables. Furthermore, the causal relationship between meditation practice and TL remains to be rigorously tested in healthy participants with a longitudinal and experimentally-controlled study design.

Although the meditation interventions studied to date have varied in length, intensity, style of practice, and target population, the available evidence suggests that meditation practice promotes adaptive psychological functioning and improved telomere maintenance. In addition to TA and TL, meditation appears to influence the expression of several telomere-related genes (TRGs) (Bhasin et al., 2013; Duraimani et al., 2015; Epel et al., 2016), yet no study has directly explored the effects of meditation on a targeted array of genes involved in the broader telomere interactome. Moreover, no study has assessed changes across all three measures of cellular aging simultaneously. Because TL, TA, and TRG expression change and function on different time scales, they are likely to provide

independent, yet complementary information regarding intervention effects (Lin et al., 2010). For example, most intervention studies that have assessed TL and TA have reported effects in one measure, but not both, suggesting that these processes may have different kinetics. Furthermore, given the aforementioned links between psychological functioning and biological processes, it is important to consider how individual differences in personality and psychological health may moderate meditation-related changes in telomere outcomes. To address these gaps in the literature, we measured changes in TL, TA, and an array of TRGs in relation to major personality traits, anxiety, and depression during a 1-month intensive Insight meditation retreat.

Within the Insight meditation tradition, practitioners engage in retreats to limit distraction and to receive guided support during periods of extended practice. While on retreat, practitioners refrain from verbal and written communication, typically eat a vegetarian diet, and are encouraged to treat all daily activities (e.g., eating, walking, simple chores) as opportunities to attend to their ongoing sensory and mental experience with open and reflexive awareness (e.g., Goldstein, 1987). From this perspective, Insight retreats can be conceived of as comprehensive well-being interventions that pair periods of formal meditation practice (e.g., sitting or walking) with a contemplative way of life or "stance toward experience" (Lutz et al., 2015). Thus, the focus of the present study was to examine the outcomes of a holistic retreat intervention that emphasizes formal meditation training.

We assessed retreat participants at the beginning of and 3 weeks into training, along with a passive control group of experienced meditators living at home. We hypothesized that both TL and TA would increase as a function of retreat participation. We also used a customized pathway-focused array to explore the expression of 54 genes central to human telomerase function and telomere replication and maintenance. We expected retreat participants to demonstrate broad patterns of change in TRG expression indicative of improved telomere and telomerase function.

We also explored the degree to which individual differences in trait-like styles of thought, feeling, and action—as captured by the five-factor personality model (John and Srivastava, 1999; McCrae and Costa, 1997)—influenced practitioners' telomere-related outcomes. Because these traits represent relatively stable and enduring aspects of one's personality, we did not have strong predictions about the effects of retreat on conscientiousness, agreeableness, openness to experience, or extroversion. However, in line with the decrease observed in Jacobs et al. (2011), we expected a retreat-related reduction in neuroticism—the tendency to experience negative emotions and emotional instability (John and Srivastava, 1999). As neuroticism has been found to predict shorter telomeres (van Ockenburg et al., 2014), we further expected decreases in neuroticism to predict improved telomere regulation. We similarly expected retreat-related reductions in anxiety and depression, and that these reductions would to correlate with improved telomere biology.

## 2. Methods

### 2.1. Participants

Retreat participants ($n$ = 28; 14 female, 13 male, 1 unspecified) were recruited from a pool of candidates pre-enrolled in one of two month-long, silent residential retreats held at Spirit Rock Meditation Center (SRMC) in Woodacre, CA (February and March). To enroll in these retreats, SRMC requires individuals to have previously completed at least two silent meditation retreats of 7 days or longer. A group of comparison participants, similar in age and gender ($n$ = 34; 23 female, 11 male), were recruited from the local SRMC community via flyers, newsletters, and presentations at weekly community meditation gatherings. Comparison[4] participants were required to have previously attended at least two 5–10 day retreats, without having attended a retreat for at least 4 weeks prior to study participation[5]. Applicants were excluded if they reported medical conditions that might influence telomere length, telomerase activity, or immune cell distributions, including cancers, autoimmune diseases, immunodeficiency disorders, or other conditions involving chronic inflammation such as hepatitis. Given the limited pool of potential participants, individuals were not excluded for use of antidepressant or anxiolytic medication[6]. Participants gave informed consent and were paid $20 per hour for their participation. The Institutional Review Board of the University of California, Davis approved all study protocols, and the study was registered on clinicaltrials.gov (#NCT03056105).

Two retreat participants withdrew after the first assessment for reasons unrelated to the intervention, and three retreat participants did not complete questionnaires at either the pre- or post-assessment point. Three control participants withdrew after the initial blood draw due to scheduling conflicts or overall time commitment, and six control participants did not complete questionnaires at one of the assessment points.

### 2.2. Meditation retreat intervention

Retreat participants were instructed in Insight meditation, a style of *vipassana* practice stemming from the Theravada Buddhist tradition, which includes both walking and sitting variations (Goldstein and Kornfield, 2001). During sitting meditation, practitioners were asked to direct their attention to physical sensations of the body (e.g., the breath) and to observe their thoughts, desires, and intentions with gentle, reflexive awareness. During walking meditation, practitioners were instructed to bring awareness to the lifting, forward movement, and placing of their feet (Goldstein, 1987). Instruction also included the Four Immeasurables (or *Brahma Viharas* in Pali), a collection of practices used to develop benevolent feelings and motivational states towards oneself and others, including loving-kindness (*metta*), compassion (*karuna*), empathetic-joy (*mudita*), and equanimity (*upekkha*) (Salzberg, 1995; Wallace, 1999).

Retreats were taught by teams of six experienced teachers and held in "noble silence," meaning participants refrained from regular verbal and written communication, as well as eye contact, except during periodic meetings with teachers. Participants lived on-site for the duration of the retreat and were provided an ovo-lacto vegetarian diet. The daily schedule included alternating periods (30–45 mins) of sitting and walking meditation, totaling roughly 10 h per day, along with work meditations (i.e., chores) and regular meal times (see Supplemental Material for daily retreat schedule). Seated meditation practice was held in a spacious meditation hall, where approximately 80 retreat participants meditated as a group, and walking meditation took place in adjoining halls or outdoors on the SRMC grounds.

### 2.3. Assessments

Retreat participants were assessed at SRMC the morning following their first full day of silent meditation, and again 3 weeks later

[4] We use the term comparison here to denote that this was not a randomized control group; for simplicity, we refer to these participants as controls hereafter.

[5] An exception was made in the case of a comparison participant who had attended a single retreat greater than 20 days in length.

[6] Although a greater number of retreat participants (17%) reported use of anxiolytic or antidepressant medications than controls (5%), controlling for medication use did not change the pattern or significance of any effects, including self-reported anxiety and depression.

(several days before ending silence). Control participants were assessed in waves from May through February of the following year, at the Anubhuti Retreat Center (Novato, CA), a similarly peaceful setting in the same geographic region. Groups of 4–12 control participants were assessed at the beginning and end of 3-week intervals, during which they maintained their normal daily routines. Retreat participants gave blood between 5:00 and 6:00 am. Control participants completed a 40-min meditation session prior to each blood collection, and gave blood between 9:00 and 10:00 am. Professional phlebotomists collected blood via antecubital venipuncture, and all participants were asked to refrain from eating for 8 h prior to the draw. Participants' weight was measured immediately before each blood collection, and their height was recorded at the second assessment. Body mass index was calculated as BMI = [Weight (lbs) * 703] / Height (in)$^2$. Following each blood collection, participants were given a packet of questionnaires, which were completed and returned to the experimenters within 36 h.

### 2.4. Blood sample preparation

Whole blood was collected in Vacutainer Cell Preparation Tubes (Becton Dickinson, Franklin Lakes, NJ) and transported at room temperature to a field lab where PBMCs were isolated by density-gradient centrifugation (Sorvall Legend) as per manufacturer's instructions (time from collection to centrifugation was less than 30 min). Cells were washed twice with Dulbecco's phosphate buffer saline and stained with Trypan Blue to count live cells using a hemocytometer. For TL measurement, ~1 million PBMCs per sample were pelleted and stored at −80 °C. For TA assays, aliquots of 0.5 million cells were pelleted and lysed with 1 × CHAPS buffer. Extracts containing 5000 cells/μl were then prepared and stored at −80 °C. Samples were subsequently delivered on dry ice to the University of California, San Francisco, where TA and TL were assayed in the laboratory of Dr. Elizabeth Blackburn. For gene expression, cell pellets of ~2 million cells were conserved in RNA Later (Sigma, St Louis, MO) and stored at −80 °C, then shipped on dry ice to the University of Barcelona for RNA extraction in the laboratory of PK.

### 2.5. Telomere length measurement

Total genomic DNA was purified from PBMCs using QIAamp DNA Mini kits (QIAGEN, Cat# 51104) and stored at −80 °C for batch TL measurement. The TL assay methodology was identical to that of Lin et al. (2010; adapted from Cawthon, 2002, 2009), with the exception that reaction mixes contained 1.78–12.6 ng of genomic DNA per 11 μl reaction.

TL is expressed as t/s, the ratio of telomeric (T) to single copy (S) gene product for a particular sample. T and S values were measured in triplicate using a real-time PCR machine with a 384-tube capacity, and then averaged before calculating the t/s ratio for a given sample from a given PCR batch or 'run'. Each sample was measured in two to five runs, resulting in two to five t/s values per sample ($M$ = 3.7 values, $SD$ = 1), which were then adjusted for inter-assay variability between runs using a normalizing factor derived from 8 different DNA samples of control cancer cell lines. These control samples were measured in quadruplicate in each present PCR batch to derive an averaged t/s value; this value was then divided by the average t/s value for the same DNA from 10 prior PCR batches to obtain a normalizing factor. This was done for all 8 control samples and the average of these normalizing factors was used to correct the participant DNA samples to get the final t/s ratios. The inter-assay coefficient of variation was 4.7%.

Steenstrup et al. (2013) have suggested that most, if not all, instances of observed telomere lengthening may be attributable to measurement error. For instance, a common analytic approach is to measure t/s ratios two or three times per sample and to average these values to obtain a single estimate of TL. However, averaging t/s ratios may obscure inter- and intra-assay variability. To better account for these sources of error, we used a multilevel modeling approach in which raw t/s values were nested within participants and assay runs.

### 2.6. Telomerase activity measurement

TA was measured using Gel-TRAP (Telomerase Repeat Amplification Protocol) assays. Reactions were carried out according to the TRAPeze Telomerase Detection Kit (Millipore, Cat# S7700) and run on 8% polyacrylamide-8 M urea sequencing gels. Gels were then exposed to a phosphorimager plate overnight and scanned on a Typhoon 8600 Imager (GE Healthcare, Piscataway, NJ). 293 T cancer cells were used as a positive TA control and standard. TA was expressed as the equivalent number of 293 T cells and quantified using ImageQuant 5.2 software (GE Healthcare, Piscataway, NJ). Signals from product ladders were added and normalized against the signal from an internal control band for the same lane of the gel to calculate the product/internal control value. For each assay reaction, the product/internal sample value was divided by the product/internal control value from twenty 293 T cells and multiplied by 20 to obtain the final TA units, where 1 unit equals the product from one 293 T cell/10,000 immune cells. The average intra-assay variability of PBMC samples was 8% (from six samples assayed in triplicate) and the inter-assay variability of PBMC samples was 6.7% (from 24 samples assayed on two different days). For both TL and TA measurement, pre- and post-assessment samples from each participant were assayed in the same batch. Batches contained approximately equal numbers retreat and control samples, and lab personnel performing assays were blind to group status.

### 2.7. Gene expression

A list of 54 telomere-related candidate genes was curated based on existing literature indicating their mechanistic role in telomere maintenance via personal communication with Dr. Blackburn. Total RNA was extracted using the mirVana™ RNA Isolation Kit (Applied Biosystems) as per manufacturer's instructions. Yield, purity, and quality of RNA were determined spectrophotometrically (NanoDrop, USA) using Bioanalyzer 2100 (Agilent Technologies) capillary electrophoresis, resulting in RNA with 260/280 nm ratios above 1.9 and RNA Integrity Numbers (RIN) higher than 7.5. Random-primed cDNA synthesis starting with 0.2 μg of RNA was performed at 37 °C using the High Capacity cDNA Archive Kit (Applied Biosystems).

Quantitative real time (q-RT) PCR was performed using a Bio-Rad CFX384 real-time PCR system and TaqMan FAM-labeled specific probes (Applied Biosystems) listed in Table S3. Duplicates were run for each sample on a 384-well plate. A pre-amplification step (Taqman PreAmp Master Mix; Applied Biosystems, Foster, CA) was performed for genes exhibiting very low levels of expression (*Ctc1, Obfc1, Terf1, Tert* and *Xrcc2*). Q-RT PCR data were analyzed with the Bio-Rad CFX Manager using the automatic setting to determine the Ct baseline and threshold. Relative expression of each gene was calculated using the $2^{-\Delta\Delta Ct}$ method after normalizing to TBP reference gene expression (Livak and Schmittgen, 2001).

### 2.8. Self-report measures (Lifestyle, distress, personality)

#### 2.8.1. Lifestyle profile II

Health responsibility (9 items), physical activity (8 items), nutrition (9 items), spiritual growth (9 items), interpersonal rela-

tions (9 items), and stress management (8 items) were assessed with the 52-item Lifestyle Profile II (Walker et al., 1987). Participants indicated the frequency with which they engaged in listed behaviors using a 4-point Likert-type scale ranging from "Never" to "Routinely." Subscale scores were averaged, with higher scores indicating more frequent engagement with a particular lifestyle factor.

*2.8.2. State trait anxiety inventory (STAI-T)*

Trait anxiety was assessed with the 10 trait items from the STAI (Spielberger et al., 1983). Respondents indicated how they felt generally over the past month on a 4-point Likert-type scale ranging from "Almost Never" to "Almost Always." Responses were summed for each participant, with higher scores indicating greater trait anxiety.

*2.8.3. Center for epidemiologic studies depression scale (CES-D)*

Depression symptoms were assessed with the 20-item CES-D scale (Radloff, 1977). Respondents indicated the frequency with which they experienced aspects of depression, such as poor appetite, restless sleep, and feeling lonely over the last month using a 4-point Likert-type scale ranging from "Rarely or none of the time (less than 1 day each week)" to "Most or all of the time (5–7 days each week)." Responses were summed for each participant yielding a possible range of 0–60, with higher scores indicating greater depressive symptoms.

*2.8.4. Big five inventory (BFI)*

Personality dimensions were assessed using the 44-item Big Five Inventory (Goldberg, 1993): extraversion (8 items), agreeableness (9 items) conscientiousness (9 items), neuroticism (8 items), and openness to experience (10 items). Respondents indicated the degree to which they agreed with the items listed on a 7-point Likert-type scale from "Strongly Disagree" to "Strongly Agree." Subscale scores were averaged, with higher scores indicating a greater degree of a given personality dimension.

*2.9. Statistical methods*

Multilevel mixed effects models (MLMs) were used to test changes in dependent measures over time and to examine relations between self-report and cell aging measures. Models assessing changes in TL, TA, TRG expression, and self-report measures included the fixed effects of group (control = 0, retreat = 1) and time (pre = 0, post = 1), and the interaction between group and time. Random effects for participants were included to allow for within-person dependency across assessments. Analyses assessing TL also included a random effect of assay run to account for variance common to samples run in the same batch. Because MLMs can accommodate missing data, participants who dropped from the study or were otherwise unable to complete all assessments were included in analyses.

Models were estimated with PROC MIXED in SAS Version 9.4 using restricted maximum likelihood. Significance of fixed effects was evaluated using Kenward-Roger approximated degrees of freedom reported to the nearest integer. Log-likelihood tests of change in model fit ($-2\Delta LL$) were used to test significance of random effects. The normality of model residuals was tested using the Shapiro-Wilk test, and homogeneity of variance was assessed by comparing models assuming equal variance to those allowing for heterogeneous variance between groups and assessment points. TA and TRG expression levels were log-transformed to meet normality assumptions.

In line with prior research (Cramer and Imaike, 2002; Müezzinler et al., 2014, 2013; Robles-Espinoza et al., 2015; Savolainen et al., 2015), age, gender, and BMI were considered as covariates in statistical models of TL and TA. Age was centered at the grand mean (50.74 years), and gender centered to female (female = 0, male = 1). In order to differentiate the effects of baseline differences in BMI from retreat-related changes in BMI, we partialed this predictor into pre-assessment BMI (centered at the grand mean, $M = 24.16$ BMI) and change in BMI (post BMI – pre BMI). Non-significant covariates were removed from models before proceeding with further analyses.

Post-hoc mean comparisons of TL, TA, and self-report measures were adjusted using the Tukey-Kramer procedure. For analyses of TRGs, pairwise comparisons of model-estimated mean differences within each group over time (post – pre) and between groups at each assessment (retreat − control) were extracted, yielding 216 total test statistics (4 comparisons × 54 genes). The pool of resultant $p$-values was then subjected to false discovery rate (FDR) control of Type I error (Reiner et al., 2003) using the two-stage linear step-up procedure of Benjamini et al. (2006). The expected proportion of false discoveries (Q) was set at .05, and observed (uncorrected) $p$-values are reported for all analyses.

## 3. Results

Participant demographics and lifestyle variables are reported in Table S1. Prior meditation experience variables are reported in Table S2. Groups did not differ in age, gender, BMI, or lifestyle factors at pre-assessment, nor in reported lifetime meditation experience, total number of retreats, or longest previously attended retreat (all $ps > .05$). Retreat participants had, however, attended significantly more days of retreat in the prior year than controls (Control $M = 10$, Retreat $M = 28$, $p = .016$). BMI decreased across assessments in retreat participants (ß = −0.632, SE = 0.13, $p < .0001$), but not in controls. Observed means and standard deviations for TL, TA, and self-report measures are reported in Table 1, with corresponding alpha reliability coefficients for each scale.

*3.1. Telomere length*

To characterize sources of variability in t/s ratios, we first fit an unconditional MLM with individual t/s values at level 1 cross-nested within participants and assay runs at level 2. There were two to five t/s values for each participant at each assessment, totaling 445 observations. Inclusion of a random intercept for participants significantly improved model fit over the unconditional model [$-2\Delta LL(1) = 681.2$, $p < .001$], as did the inclusion of a random intercept for assay variability [$-2\Delta LL(1) = 73.1$, $p < .001$]. The intraclass correlation coefficient (ICC) for the participant intercept was 0.86, suggesting that 86% of the total variance in t/s values was attributable to differences between individuals. The ICC for assay run indicated that 3% of the variance in t/s ratio was due to variability between assay runs, leaving 11% of the total variance attributable to unexplained within-person or within-assay factors. Although the majority of variance in t/s ratios was attributable to differences between, rather than within, individuals, assay run explained an additional 3% of variance that would otherwise contribute residual error to the data, highlighting the utility of using this modeling approach.

Next, we examined retreat-related changes in TL. There was no effect of group [$F(1, 59) = 2.22$, $p = .141$], but there was a significant effect of time [$F(1, 377) = 9.12$, $p = .003$] and a significant interaction between group and time [$F(1, 378) = 11.65$, $p < .001$], such that retreat participants showed an estimated increase of 0.046 units in t/s ratios across assessments [$p < .001$, 95% CI (0.019, 0.072)], compared to controls. Mean comparisons affirmed a statistically significant increase of 0.043 units within the retreat group from pre- to post-assessment [$p < .001$, 95% CI (0.024, 0.063)], reflecting an

**Table 1**
Descriptive statistics for telomere length, telomerase activity, and self-report measures.

| | Pre-assessment | | | | | Post-assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Control | | Retreat | | | Control | | Retreat | |
| | Alpha | *n* | Mean (*SD*) | *n* | Mean (*SD*) | Alpha | *n* | Mean (*SD*) | *n* | Mean (*SD*) |
| Telomere length (t/s) | | 132 | 1.11 (0.19) | 106 | 1.16 (0.24) | | 110 | 1.10 (0.19) | 106 | 1.22 (0.27) |
| Telomerase activity (ln) | | 32 | 10.57 (7.86) | 28 | 8.26 (6.73) | | 27 | 9.09 (7.73) | 26 | 6.21 (3.08) |
| Personality (BFI; 1–7) | | | | | | | | | | |
| Neuroticism | 0.90 | 30 | 3.4 (1.4) | 26 | 3.6 (1.2) | 0.89 | 27 | 3.1 (1.4) | 25 | 3.5 (1.1) |
| Agreeableness | 0.71 | 30 | 5.2 (0.9) | 26 | 5.5 (0.5) | 0.77 | 27 | 5.4 (0.9) | 25 | 5.7 (0.6) |
| Conscientiousness | 0.85 | 30 | 5.5 (1.0) | 26 | 5.5 (1.0) | 0.86 | 27 | 5.3 (1.0) | 25 | 5.6 (09) |
| Openness | 0.80 | 30 | 5.5 (0.8) | 26 | 5.5 (0.7) | 0.78 | 27 | 5.6 (0.8) | 25 | 5.6 (0.8) |
| Extraversion | 0.81 | 30 | 4.5 (1.1) | 26 | 4.3 (1.0) | 0.79 | 27 | 4.6 (0.8) | 25 | 4.3 (1.0) |
| Trait anxiety (STAI; 1–4) | 0.94 | 30 | 38.3 (11.3) | 28 | 38.2 (9.4) | 0.94 | 27 | 38.0 (12.0) | 25 | 35.2 (6.7) |
| Depression (CES-D; 0–3) | 0.89 | 30 | 13.0 (9.1) | 27 | 13.5 (8.4) | 0.88 | 27 | 13.9 (11.1) | 25 | 13.5 (6.9) |

*Note*: For telomere length, *n* corresponds to the number of t/s values (across runs) used in multilevel analyses; for all other measures *n* corresponds to the number of participants. The number of participants for telomere length is equivalent to the number of subjects for whom telomerase values are available at each assessment. Converting t/s ratios to base pairs [bp = 3274 + 2413 * (t/s)] and then dividing by 1000 yields the following mean estimates in kilo base pairs (kbp): Control = 5.95 kbp at pre-assessment and 5.93 kbp at post-assessment; Retreat = 6.07 kbp at pre-assessment and 6.22 kbp at post-assessment.

apparent increase in TL of approximately 104.2 base pairs (bp)[7]. There was no change in controls (all *ps* > .05), and no significant difference between groups at either assessment. Finally, we examined the effects of person-level covariates on t/s ratios. Age, gender, and BMI (change and baseline) each predicted TL when entered separately into the model (see Table S4 for model parameters). However, BMI was not a significant predictor of t/s ratios when BMI and gender were both included as predictors; thus, the final model assessing TL included only age and gender as covariates (see Base Model in Table S5). Parameter estimates indicated that each year of age corresponded to a decrease in TL of −0.009 units [$p < .001$, 95% CI (−0.013, −0.006)], and that male TL was, on average, −0.135 units [$p = .001$, 95% CI (−0.214, −0.055)] shorter than females, consistent with other studies (Gardner et al., 2014; Robles-Espinoza et al., 2015). Importantly, the interaction between group and time remained significant after controlling for covariates in this model [$F(1, 372) = 12.89$, $p < .001$].

### 3.2. Telomerase activity

Contrary to our hypotheses, there was no significant effect of time [$F(1, 57) = 2.59$, $p = .113$] or interaction between group and time [$F(1, 57) < 0.01$, $p = .975$] on TA. We did observe a significant main effect of group [$F(1, 60) = 4.76$, $p = .033$], such that the control group had higher levels of TA across assessments (Fig. 1); however, post-hoc comparisons indicated that the difference between groups was not significant at either assessment (*ps* > .05). Neither age [ß = −0.002, 95% CI (−0.013, 0.008)] nor gender [ß = 0.073, 95% CI (−0.199, 0.345)] significantly predicted TA when covariates were included in the model. Similarly, neither pre-assessment BMI [ß = −0.007, 95% CI (−0.042, 0.03)] nor change in BMI [ß = 0.251, 95% CI (−0.031, 0.534)] predicted TA; however when included, these predictors eliminated the previously observed group difference.

### 3.3. Relations between telomerase activity, telomere length, and retreat experience

In line with previous studies (Lin et al., 2016, 2010), TL and TA were not significantly correlated at either pre- [$r(58) = .17$, $p = .198$] or post-assessment [$r(51) = -.19$, $p = .163$] in the overall sample. Changes in TA were also uncorrelated with changes in TL across assessments [$r(49) = .09$, $p = .545$]. However, baseline TA was negatively correlated with changes in TL across assessments, such that lower TA at pre-assessment was associated with greater increases in TL across groups [$r(52) = -.28$, $p = .043$]. This correlation was significant in retreat participants when considered separately [$r(24) = -.41$, $p = .038$], but not in controls [$r(26) = -.12$, $p = .552$]. To further characterize this relationship, we entered TA, time, and the interaction between TA and time into a model predicting TL in retreat participants only, with age and gender included as covariates. This model revealed a significant interaction between TA and time [$F(1, 167) = 10.63$, $p = .001$]. According to simple slope estimates, retreat participants with baseline TA levels at the retreat-group mean [ß = 0.045, 95% CI (0.025, 0.065)] or 1 SD below the retreat-group mean [ß = 0.091, 95% CI (0.059, 0.123)] were estimated to have significant increases in TL across assessments.

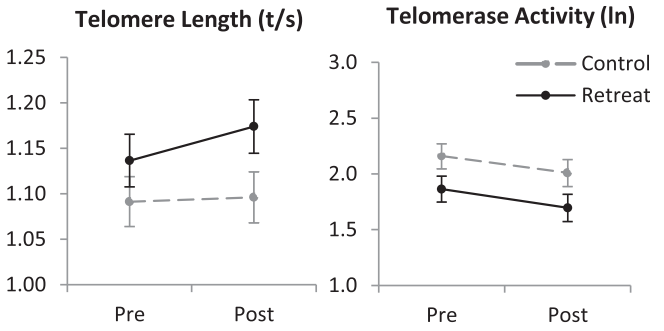


**Fig. 1.** Change in telomere length and telomerase by group. Error bars represent standard error.

We also explored relations between TA, TL, and retreat participants' reports of practice engagement during the retreat intervention (see Supplemental Material for a full description of practice engagement measures, and supplemental correlations with lifetime meditation experience variables). Changes in TL were positively correlated with retreat participants' reports of how diligently they felt they had practiced in relation to their peers [Spearman $r_s(22) = .42$, $p = .039$], whereas TA levels at post-assessment—but not changes in TA—were negatively correlated with reports of practice diligence [$r_s(22) = -.57$, $p = .003$]. TA at post-assessment was also negatively correlated with retreat participants' estimates of the number of hours they had spent meditating during retreat [$r(23) = -.43$, $p = .033$].

[7] The formula bp = 3274 + 2413 * (t/s) was used to convert t/s ratios to base pairs (72), which was derived from a direct comparison of qPCR t/s ratios and Southern blot analyses performed in the lab of Dr. Blackburn on a set of DNA samples from cultured human fibroblasts.

### 3.4. Telomere-related genes

To explore molecular mechanisms underlying patterns of TL and TA, we investigated retreat-related changes in 54 candidate genes. Significant model-estimated pairwise comparisons and resultant *p*-values are presented in Table 2; non-significant gene results are presented in Table S6. Significance was evaluated at an FDR threshold of .018 across all tests; *p*-values below this threshold are interpreted as discoveries.

Retreat participation appeared to impact group differences in gene expression across assessments: of the 54 candidate genes, only six (11%) showed group differences at pre-assessment (*Cct2, Cct4*, *Terf1*, *Terf2*, *Upf3b*, *Xrn1*), whereas 24 (44%) showed group differences at post-assessment (see Table 2). The retreat group exhibited significant changes in 17 genes (31%) that did not differ between groups at pre-assessment. Of this subset, *Atrip*, *Cct1*, *Cct6*, *Gar1*, and *Hnrnpa1* showed increased expression levels in retreat participants but not controls, whereas *Nabp1*, *Pot1*, *Wrap53*, *Xrcc3*, and *Xrcc4* showed decreases in retreat participants only. Seven genes showed changes in both groups: *Cct1* and *Nabp2* increased in retreat participants but decreased in controls; *Upf1* decreased in both groups, with significantly lower expression in retreat participants at post; and *Atmin*, *Nhp2*, *Tep1*, and *Tinf2* changed in both groups, but did not differ at post-assessment.

An additional 11 genes (*Atm*, *Atr*, *Atrx*, *Cct2*, *Cct7*, *Cct8*, *Dkc1*, *Obfc1*, *Upf3a*, *Xrcc6*, *Xrcc6bp1*) showed decreased expression levels in controls only. Significant group differences were observed at post-assessment for eight of these genes. Of these, only *Cct2* showed a significant group difference at pre-assessment. There were no significant changes in the remaining 28 genes for either group.

### 3.5. Self-report measures

We assessed changes in self-report measures across groups and assessments, observing significant group by time interactions for trait anxiety [$F(1,51) = 5.18$, $p = .027$; Fig. S1] and conscientiousness [$F(1,48) = 11.43$, $p = .001$, Fig. S2] only. Post-hoc comparisons revealed a significant decrease in trait anxiety [ß = −3.79, 95% CI (−7.24, −0.34)] and an increase in conscientiousness [ß = 0.26, 95% CI (0.05, 0.48)] in the retreat group, but no changes in controls and no significant differences between groups at either assessment (all *ps* > .05). There were also significant main effects of time for neuroticism [$F(1,49 = 6.49$, $p = .014$] and agreeableness [$F(1,51) = 4.07$, $p = .05$]. Neuroticism decreased [ß = −0.21, 95% CI (−0.38, −0.04)] whereas agreeableness increased [ß = 0.29, 95% CI (0.001, 0.27)] in both groups from pre- to post-assessment (Fig. S2). No significant effects were observed for openness, extraversion, or depression (all *ps* > .05).

### 3.6. Relations of self-report measures to telomere length and telomerase activity

Inspection of individual change scores revealed substantial variability in the magnitude of TL changes (Fig. S3). To better characterize these individual differences, we fit a series of models assessing relations of self-reported personality factors, anxiety, and depression with TL and TA.

We first assessed the main effects of self-report variables in predicting TL overall (i.e., across assessments and groups). Each self-report predictor was added to a separate model including fixed effects of group, time, and the group by time interaction, with age and gender as covariates (Table S5). Anxiety [ß = −0.002, 95% CI (−0.004, −0.001)] and depression [ß = −0.002, 95% CI (−0.005, −0.0002)] each significantly predicted TL, with higher levels relating to shorter TL. There was a similar, yet non-significant, effect of neuroticism [ß = −0.019, 95% CI (−0.039, 0.001)]. No effects were observed for agreeableness, openness, conscientiousness, or extraversion.

Next, we assessed whether self-report measures interacted with group and time to predict TL. Significant three-way interactions were found for neuroticism, agreeableness, and openness (Table S5). To interpret these interactions, we estimated simple slopes at 1 SD below and 1 SD above the self-report mean for each significant interaction. As shown in Fig. 2, model estimates indicated greater TL increases in retreat participants 1 SD above the mean in neuroticism [ß = 0.094, 95% CI (0.052, 0.136)] or 1 SD below the mean in agreeableness [ß = 0.138, 95% CI (0.081, 0.194)]. By contrast, estimates indicated little change in TL for individuals 1 SD below the mean in neuroticism [ß = −0.018, 95% CI (−0.068, 0.033)] or above the mean in agreeableness [ß = −0.009, 95% CI (−0.054, 0.036)]. Model estimates also indicated telomere lengthening in retreat participants who were 1 SD above the mean in openness [ß = 0.077, 95% CI (0.035, 0.119)]—but shortening in controls [ß = −0.040, 95% CI (−0.077, −0.003)].

Parallel analyses were conducted with TA as the outcome variable. In these models, no psychological variable predicted TA as a main effect. When interaction effects were added, we observed significant two-way interactions between neuroticism and group [$F(1,69) = 7.45$, $p = .008$] and neuroticism and time [$F(1,49) = 11.01$, $p = .002$], but a non-significant three-way interaction between neuroticism, group, and time [$F(1,49) = 3.27$, $p = .077$]. Simple slopes, depicted in Fig. S4, show a significant decline in TA from pre- to post-assessment in retreat participants 1 SD below the mean in neuroticism [ß = −0.780, 95% CI (−1.334, −0.226)]. For participants 1 SD above the mean in neuroticism, estimates indicated that retreat participants had significantly lower TA at pre-assessment [ß = −0.703, 95% CI (−1.286, −0.131)], but did not significantly differ from controls at post-assessment. Thus, retreat participants who entered retreat low in neuroticism seem to have decreased in TA, while those higher in neuroticism seem to have shown a subtle increase, which is logically consistent with the pattern of observed telomere results.

These analyses suggest that both agreeableness and openness moderate retreat-related changes in TL, while neuroticism appears to moderate changes in both TL and TA. However, because these models included self-report variables as time-varying predictors, we could not differentiate whether changes in TL or TA were driven by interindividual differences in baseline personality measures, or by intraindividual changes across retreat. Therefore, for each self-report index, we partialed baseline self-report values (pre-assessment scores, centered at the grand mean) from changes in self-report (post – pre difference scores). We then entered these new variables as predictors in models of changes in TL or TA (post – pre difference scores) for retreat participants only. A significance criterion of .025 was used to adjust for potential inflation of Type I error that can result from using dependent baseline and change scores as simultaneous predictors.

Baseline neuroticism [$F(1, 21) = 9.80$, $p = .005$] and agreeableness [$F(1,21) = 9.51$, $p = .006$] each significantly predicted change in TL across retreat. Neuroticism was positively related to change in TL: individuals who entered retreat with higher neuroticism scores showed greater increases in TL across retreat (Table 3; Fig. S5, top). This finding does not appear to be the result of a floor effect—wherein individuals higher in neuroticism had greater room for improvement due to shorter telomeres at baseline—as neuroticism and TL were unrelated at pre-assessment [$r(24) = -0.23$, $p = .263$]. Baseline neuroticism was also positively related to changes in TA across retreat [$F(1, 21) = 10.47$, p = .004; Table 3], consistent with the patterns observed in Fig. S4. Baseline agreeableness, on the other hand, was negatively related to changes in TL, such that participants who entered retreat with lower agreeableness scores were more likely to show increased

**Table 2**
Estimated mean differences in gene expression by group and assessment: significant discoveries.

| Gene | Summary of discoveries | | *p*-value, uncorrected | | | | Estimated mean difference (*SE*) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Change over time | Group difference | Time (Post – Pre) | | Group (Control – Retreat) | | Time (Post – Pre) | | Group (Control – Retreat) | |
| | | | Retreat | Control | Pre | Post | Retreat | Control | Pre | Post |
| Atrip | R↑ | | .011 | .054 | .692 | .222 | 0.412 (0.157) | 0.276 (0.140) | −0.059 (0.148) | −0.194 (0.158) |
| Cct1 | R↑ | Post (R > C) | .003 | .609 | .139 | <.001 | 0.259 (0.082) | 0.039 (0.076) | −0.121 (0.081) | −0.341 (0.086) |
| Cct6 | R↑ | Post (R > C) | <.001 | .052 | .389 | .001 | 0.605 (0.138) | 0.252 (0.127) | −0.118 (0.137) | −0.471 (0.144) |
| Gar1 | R↑ | | .010 | .028 | .588 | .247 | 0.429 (0.160) | 0.322 (0.143) | −0.083 (0.154) | −0.190 (0.163) |
| Hnrnpa1 | R↑ | | .005 | .021 | .085 | .022 | 0.518 (0.179) | 0.394 (0.165) | −0.309 (0.178) | −0.434 (0.187) |
| Atmin | R↑, C↑ | | <.001 | .006 | .857 | .233 | 0.725 (0.202) | 0.513 (0.181) | −0.035 (0.194) | −0.248 (0.207) |
| Nhp2 | R↑, C↑ | | .004 | .005 | .399 | .244 | 0.353 (0.119) | 0.309 (0.106) | −0.094 (0.111) | −0.139 (0.118) |
| Ctc1 | R↑, C↓ | Post (R > C) | .012 | .016 | .197 | .002 | 0.425 (0.164) | −0.364 (0.147) | 0.222 (0.171) | −0.567 (0.178) |
| Nabp2 | R↑, C↓ | Post (R > C) | .002 | <.001 | .112 | <.001 | 0.157 (0.050) | −0.172 (0.046) | −0.142 (0.088) | −0.471 (0.090) |
| Nabp1 | R↓ | Post (C > R) | <.001 | .075 | .442 | <.001 | −0.257 (0.036) | −0.061 (0.034) | 0.038 (0.049) | 0.233 (0.050) |
| Pot1 | R↓ | | .017 | .036 | .931 | .670 | −0.124 (0.050) | −0.097 (0.045) | −0.004 (0.050) | 0.023 (0.054) |
| Wrap53 | R↓ | | .006 | .057 | .842 | .495 | −0.176 (0.061) | −0.106 (0.055) | −0.015 (0.076) | 0.055 (0.080) |
| Xrcc3 | R↓ | | .017 | .023 | .577 | .796 | −0.123 (0.050) | −0.104 (0.045) | −0.036 (0.065) | −0.018 (0.068) |
| Xrcc4 | R↓ | Post (C > R) | <.001 | .443 | .242 | .014 | −0.188 (0.053) | 0.038 (0.049) | −0.070 (0.060) | 0.156 (0.063) |
| Tep1 | R↓, C↓ | | .003 | .008 | .746 | .437 | −0.138 (0.045) | −0.112 (0.040) | 0.017 (0.054) | 0.044 (0.057) |
| Tinf2 | R↓, C↓ | | .006 | .016 | .588 | .993 | −0.131 (0.046) | −0.103 (0.041) | −0.027 (0.050) | 0.000 (0.053) |
| Upf1 | R↓, C↓ | Post (R > C) | .011 | <.001 | .282 | .006 | −0.117 (0.044) | −0.209 (0.041) | −0.054 (0.050) | −0.146 (0.053) |
| Atm | C↓ | Post (R > C) | .132 | .004 | .247 | <.001 | 0.086 (0.056) | −0.157 (0.052) | −0.069 (0.060) | −0.313 (0.063) |
| Atr | C↓ | Post (R > C) | .078 | .014 | .965 | .003 | 0.064 (0.035) | −0.083 (0.033) | 0.002 (0.045) | −0.145 (0.047) |
| Atrx | C↓ | Post (R > C) | .559 | .001 | .489 | .013 | −0.023 (0.039) | −0.124 (0.036) | −0.036 (0.052) | −0.138 (0.054) |
| Cct2 | C↓ | Both (R > C) | .268 | .012 | .003 | <.001 | 0.059 (0.053) | −0.127 (0.049) | −0.186 (0.061) | −0.373 (0.063) |
| Cct7 | C↓ | Post (R > C) | .163 | .005 | .282 | <.001 | 0.089 (0.063) | −0.167 (0.058) | −0.068 (0.063) | −0.324 (0.066) |
| Cct8 | C↓ | Post (R > C) | .235 | .003 | .106 | <.001 | 0.071 (0.059) | −0.167 (0.055) | −0.148 (0.091) | −0.386 (0.093) |
| Dkc1 | C↓ | | .512 | <.001 | .430 | .086 | −0.027 (0.041) | −0.143 (0.037) | 0.035 (0.044) | −0.081 (0.047) |
| Obfc1 | C↓ | Post (R > C) | .044 | .017 | .069 | .013 | 0.204 (0.099) | −0.220 (0.089) | 0.175 (0.095) | −0.249 (0.099) |
| Upf3a | C↓ | | .204 | <.001 | .992 | .034 | −0.096 (0.075) | −0.323 (0.069) | −0.001 (0.102) | −0.228 (0.106) |
| Xrcc6 | C↓ | Post (R > C) | .361 | <.001 | .557 | <.001 | 0.039 (0.042) | −0.137 (0.039) | −0.029 (0.049) | −0.205 (0.051) |
| Xrcc6bp1 | C↓ | | .815 | <.001 | .636 | .023 | −0.011 (0.045) | −0.247 (0.042) | 0.039 (0.083) | −0.197 (0.085) |
| Cct3 | | Post (R > C) | .033 | .061 | .053 | <.001 | 0.143 (0.065) | −0.116 (0.060) | −0.159 (0.081) | −0.418 (0.085) |
| Cct4 | | Pre (C > R) | .273 | .021 | .008 | .084 | −0.052 (0.047) | −0.100 (0.042) | 0.152 (0.056) | 0.104 (0.059) |
| Hmbox1 | | Post (R > C) | .028 | .053 | .304 | <.001 | 0.124 (0.055) | −0.101 (0.051) | −0.093 (0.090) | −0.317 (0.092) |
| Smg5 | | Post (R > C) | .088 | .150 | .124 | <.001 | 0.100 (0.057) | −0.078 (0.053) | −0.134 (0.086) | −0.311 (0.089) |
| Terf1 | | Pre (C > R) | .184 | .216 | .010 | .995 | 0.192 (0.143) | −0.160 (0.129) | 0.351 (0.134) | −0.001 (0.139) |
| Terf2 | | Both (R > C) | .024 | .582 | .001 | <.001 | 0.083 (0.036) | −0.018 (0.033) | −0.221 (0.065) | −0.323 (0.067) |
| Upf2 | | Post (R > C) | .061 | .131 | .455 | .001 | 0.088 (0.046) | −0.064 (0.042) | −0.041 (0.055) | −0.193 (0.058) |
| Upf3b | | Both (R > C) | .184 | .720 | .015 | <.001 | 0.096 (0.071) | −0.024 (0.066) | −0.188 (0.076) | −0.308 (0.080) |
| Xrn1 | | Both (R > C) | .660 | .346 | .001 | <.001 | −0.019 (0.044) | −0.039 (0.041) | −0.216 (0.065) | −0.235 (0.067) |

*Note*: Statistical significance was assessed at the FDR-adjusted threshold of $\alpha = .018$ for log-transformed gene expression levels. Change over time indicates significant increases (↑) or decreases (↓) in the Retreat (R) or Control (C) group across assessments. Pre indicates a group difference at pre-assessment, Post at post-assessment, and Both at both assessments. The > symbol is used to indicate which group showed greater expression levels. Estimated mean differences for genes showing no significant discoveries are presented in Table S6.

TL (Table 3; Fig. S5, bottom). Both neuroticism [ß = 0.023, 95% CI (0.008, 0.037)] and agreeableness [ß = −0.062, 95% CI (−0.094, −0.029)] remained significant predictors of TL when entered into the model simultaneously, indicating that these variables independently predicted change in TL. Interestingly, although baseline neuroticism and agreeableness predicted changes in TL and TA, *changes* in self-reported personality measures were unrelated to changes in TL or TA.

## 4. Discussion

To our knowledge, this study is the first to report an apparent increase in TL within a 3-week intervention period, suggesting that meditation retreats may be a powerful method for improving cellular longevity. In addition to increased TL, we found that changes in TL as well as patterns of TA were moderated by individual differences in personality. We also observed retreat-related changes in the expression of a number of genes implicated in telomere biology, including those that promote intracellular trafficking of telomerase; correct folding of telomerase cofactors; and the replication, repair, and maintenance of telomeres.

### 4.1. Increased telomere length

The mean TL increase observed among retreat participants in our study was equivalent to approximately 104.2 bp. A systematic review of the relationship between age and leukocyte TL across 129 studies revealed an average yearly telomere loss of 24.7 bp (Müezzinler et al., 2014). Consistent with this literature, TL in the present study was estimated to shorten by an average of 22.9 bp for each additional year of age. Thus, the apparent telomere increase observed in the retreat group was equivalent in magnitude to the decline typically observed over about 4 years of aging. Although these findings support the view that retreat participation may boost physiological outcomes related to healthy aging, it is unknown whether this short-term increase is maintained beyond the intervention period. It is also important to note that, due to differences in assay methodology and reference standards, the conversion factors used to estimate base pairs from t/s ratios vary between labs; therefore, comparisons should be interpreted cautiously. Nevertheless, as a proof-of-concept, our findings demonstrate the malleability of TL, given the dramatic increase observed in just 3 weeks.

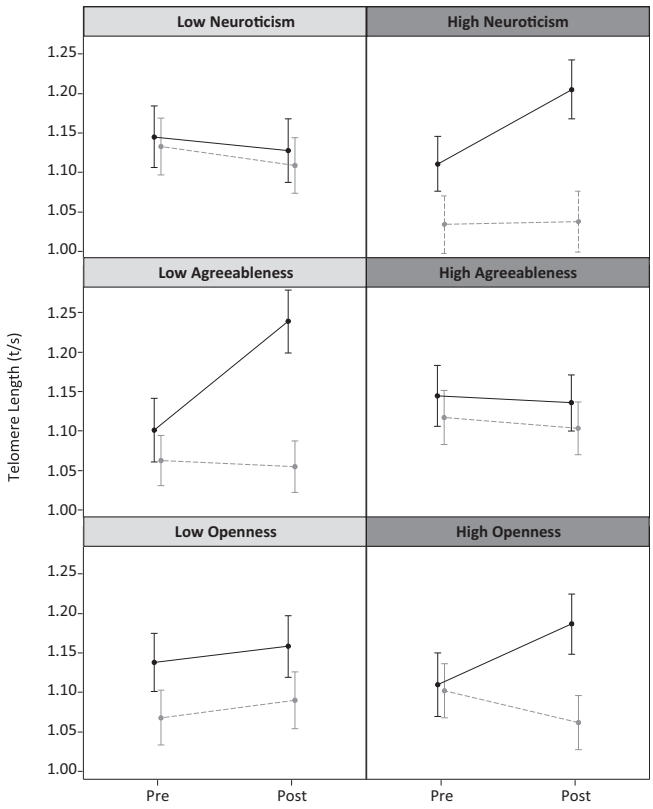


**Fig. 2.** Simple slopes for personality effects on telomere length. Plots depict model estimates 1 SD below (Low) and 1 SD above (High) the personality variable means. Error bars represent standard error. Black solid lines represent the retreat group, and grey dashed lines represent controls.

### 4.2. Telomerase activity

In contrast to the results of Jacobs et al. (2011), in which retreat participants had greater levels of TA than controls at the end of the intervention, we observed slightly higher levels of TA in controls overall—though this difference was not statistically significant at pre- or post-assessment. Epel et al. (2016) also found lower levels of TA in experienced meditators compared to meditation-naive individuals at baseline. Interestingly, we found that retreat participants' TA levels at post-assessment were inversely related to measures of retreat engagement (Results section 3.3), and to indices of prior meditation experience (Supplemental Material). Practitioners who were more experienced tended to have lower telomerase levels after 3 weeks of retreat. Retreat participants also reported greater amounts of retreat practice (in days) over the prior year. One possible explanation for this pattern of lowered TA but longer TL is that experienced meditators may require less TA to maintain optimal TL, because they are able to mitigate the effects of stressful situations before incurring telomere damage. This hypothesis is supported by a recent study showing that higher allostatic load and impoverished psychosocial resources are related to the opposite pattern of telomere biology, that is shorter telomeres and higher telomerase levels (Zalli et al., 2014). However, in the present study, both groups were drawn from a pool of experienced meditators, and thus we can only speculate regarding the small group difference in TA. Moreover, group assignment was not randomized, making it difficult to completely rule out pre-existing group differences, including possible lifestyle factors that enabled retreat participants to leave work and family commitments for a month-long retreat.

Given the heterogeneity of TA findings in the literature, it is difficult to discern a clear relationship between meditation practice and TA across studies. Many studies reporting an increase in TA have used one-tailed statistical tests, assuming that TA will increase with meditation practice. However, the present results and those of Epel et al. (2016) suggest that TA may be lower, or even decline, in some meditation practitioners. It is also notable that several studies have reported significant findings in active control groups, suggesting TA may not be sensitive to meditation specifically, but to health-enhancing interventions more generally (Carlson et al., 2015; Daubenmier et al., 2012; Duraimani et al., 2015). Finally, these contradictory findings may be an artifact of the different timescales at which TA has been measured across studies. TA is labile and can change on the order of an hour (Epel et al., 2010). Thus, it is plausible that the measurement occasions in the current study—spaced three weeks apart—masked short-term changes in TA that may have, nonetheless, contributed to observed increases in TL. For example, experienced meditation practitioners may have lower baseline levels of telomerase that increase within the first week of a retreat (in line with Epel et al., 2016), and then decline again once telomeres have been lengthened. This notion is supported by the observation that TL increases in our data were related to lower baseline telomerase levels. Rapid changes in TA may also explain the lack of correlation between TA and TL at any single assessment, as observed here and elsewhere (Lin et al., 2016, 2010). To better elucidate dynamic changes in TA across interventions, future studies will benefit from incorporating active control groups, two-tailed statistical tests, and additional assessment points with multiple samples collected at each assessment.

### 4.3. Telomere-related gene expression

Although we did not detect changes in TA across retreat, we did observe significant changes in the expression of several genes that

**Table 3**
Changes in telomere length and telomerase predicted by neuroticism and agreeableness.

| Estimate | Change in telomere length | | Change in telomerase activity | |
|---|---|---|---|---|
| | Neuroticism | Agreeableness | Neuroticism | Agreeableness |
| Intercept | 0.048 (0.015)$^{**}$ | 0.067 (0.015)$^{***}$ | −0.345 (0.139) | −0.207 (0.185) |
| Personality at pre-assessment | 0.042 (0.013)$^{**}$ | −0.082 (0.027)$^{**}$ | 0.407 (0.126)$^{**}$ | −0.345 (0.322) |
| Personality change | 0.041 (0.023) | −0.048 (0.034) | −0.196 (0.214) | 0.320 (0.409) |
| Fit statistics | | | | |
| −2 log likelihood | −44.6 | −47.5 | 51.4 | 57.3 |
| AIC | −42.6 | −45.5 | 51.6 | 59.3 |
| BIC | −41.6 | −44.5 | 52.4 | 60.3 |

*Note*: Models predicting changes (post − pre) in telomere length and telomerase activity from baseline personality and changes in personality (post − pre). Personality predictors are indicated by column subheadings. Model estimates and standard errors (in parentheses) are given for fixed effects of the intercept, personality at baseline, and changes in personality. $^{*}p \leq 0.25$, $^{**}p \leq 0.01$, $^{***}p \leq 0.001$.

encode proteins involved in the telomerase holoenzyme and its assembly, including *Gar1*, *HnRNPA1*, and *Dkc1* (Ford et al., 2002; see Wu et al., 2017 for review and illustration). Both *Gar1* and *HnRNPA1* significantly increased in the retreat group, while *Dkc1* decreased in controls. *Wrap53* expression also significantly decreased in the retreat group. Wrap53 (also called TCAB1; Freund et al., 2014) is a protein in the Cajal body that binds to telomerase *hTR* RNA and is important for assembly of the telomerase holoenzyme (Venteicher et al., 2009). Mutations in the *Wrap53* gene cause dyskeratosis congenita, a genetic disease characterized by short telomeres (Zhong et al., 2011). Interestingly, despite the observed decrease in *Wrap53* expression, retreat participants also showed relatively higher expression of multiple components of the TriC complex (*Cct1*, *Cct2*, *Cct3*, *Cct6*, *Cct7*, *Cct8*), which is required for Wrap53 folding. This contrast between *Wrap53* and TriC complex gene expression suggests that retreat participation may lead to dynamic changes in the regulation of telomerase-cofactor folding and telomerase trafficking, which are required for telomerase-mediated telomere elongation.

Retreat participants also showed higher expression levels of *CTC1*, *UPF3A*, *UPF1*, *ATRX*, *ATM*, and *ATR*, which are involved in telomere replication, repair, and maintenance. CTC1 is a component of the CST complex (CTC1-STN1-TEN1), which functions in telomere replication. CTC1 is essential for TL maintenance due to its role in mediating C-strand fill-in (Feng et al., 2017). UPF3A and UPF1 are components of the nonsense-mediated RNA decay pathway (NMD) involved in telomere replication (Lew et al., 1998). UPF1 interacts both with telomerase and the telomeric factor TPP1. UPF1 sustains telomere leading-strand replication, and its depletion leads to telomere instability owing largely to inefficient telomere leading-strand replication (Chawla et al., 2011). ATRX is a chromatin-remodeling factor that acts on telomeres. It inhibits alternative lengthening of telomeres (ALT)—a telomerase-independent telomere-lengthening pathway—and may, therefore, promote telomerase-dependent TL regulation (Clynes et al., 2015; Napier et al., 2015). ATM and ATR are DNA-damage-response protein kinases (PIKK) that phosphorylate shelterin components, and their depletion reduces telomerase complex assembly. They are also required for the recruitment of telomerase to telomeres, making them crucial for telomerase-mediated telomere maintenance (Tong et al., 2015). ATRIP, which increased in retreat participants, interacts with both ATM and ATR (Doksani and de Lange, 2014). Collectively, these findings support the conclusion that retreat participants experienced improved telomerase-mediated telomere lengthening or maintenance, despite the lack of observable change in TA.

There were also differences in the expression of genes involved in the non-homologous end-joining (NHEJ) pathway (*Xrcc3*, *Xrcc4*, *Xrcc6*, and *Xrcc6bp1*). This pathway is implicated in the repair of dysfunctional telomeres, which may otherwise result in telomere fusions (Doksani and de Lange, 2014). Expression of *Xrcc3* and *Xrcc4* decreased in retreat participants, while *Xrcc6* and *Xrcc6bp1* decreased in controls. Interestingly, cells defective in Xrcc4 do not show changes in telomere length or function, which suggests that this protein may not be involved in telomere maintenance (Yasaei and Slijepcevic, 2010); however, *Xrccr4* is a DNA repair gene that shows a linear, age-related increase in expression in human fibroblast from older females (Kalfalah et al., 2015). Thus, its decrease in retreat participants might signal some other mechanism of cell rejuvenation.

Finally, we observed changes in genes coding for OB-fold proteins, which are involved in single-strand DNA binding and telomere protection. Retreat participants showed a relative increase in the expression of *Obfc1* and *Obfc2B/Nabp2*, but a decrease in *Obfc2A/Nabp1*, which is in the same SOSS (sensor of single-strand DNA) complex as OBFC2B. *Pot1*, which is a negative regulator of TL (Lei et al., 2004, 2003; Nandakumar et al., 2012), also decreased in retreat participants.

In sum, these gene expression changes suggest that meditation retreat participation may positively influence various processes related to cell aging, including telomere maintenance and telomerase assembly and function. This profile of results further suggests that the apparent increases observed in TL may have resulted from both telomerase-mediated and telomerase-independent pathways. Future studies will be needed to replicate these findings and to differentiate these mechanisms.

### 4.4. Personality and telomere length changes

In a recent review on personality and physical health, Murray and Booth (2015) reported that conscientiousness is largely associated with better health-related outcomes, and neuroticism with worse health-related outcomes. The authors also found little evidence for a link between agreeableness and health, and heterogeneous results with regard to extraversion and openness. In the present study, we observed a significant decrease in neuroticism across groups, which was largely driven by changes in retreat participants. However, baseline levels of neuroticism—not changes in neuroticism—positively predicted changes in TL across retreat. Neuroticism concerns how easily or often a person becomes upset or distressed, and is closely related to constructs of anxiety and depression (Carver and Connor-Smith, 2010). As such, one interpretation for our results is that residential retreats may afford individuals vulnerable to negative emotional reactivity a stable and supportive environment in which to attend to their ongoing experiences and to develop adaptive coping strategies. This combination of factors may slow cellular degradation or promote restoration.

Although TL was significantly related to both anxiety and depression overall, neither baseline anxiety nor retreat-related decreases in anxiety predicted changes in TL. Despite the conceptual relatedness of neuroticism, anxiety, and depression (all *r*s >.6 in the present sample), our results point to heterogeneity in their consequences for telomeric regulation. For example, neuroticism is thought to index aspects of hostility and impulsiveness unrelated to depression, while depression includes somatic components not captured by personality scales (Luchetti et al., 2014). More research will be needed to delineate how the facets of each of these constructs relate to markers of cell aging.

We also provide novel evidence suggesting agreeableness may contribute to health outcomes. Although agreeableness increased across both groups, participants who were lowest in agreeableness at baseline were more likely to show a retreat-related increase in TL. Agreeableness tends to modulate interpersonal reactions, such that individuals higher in agreeableness become less upset over others' transgressions, whereas those low in agreeableness may become more aggressive and antagonistic (Meier and Robinson, 2004; reviewed in Carver and Connor-Smith, 2010). As with individuals high in neuroticism, those low in agreeableness may derive greater telomere-related benefits from the reduced social interaction characteristic of silent retreat.

Finally, while our findings do not support a link between conscientiousness and health, they do support a nuanced relationship between health and openness to experience. High levels of openness moderated changes in TL, such that retreat participants showed apparent telomere lengthening, while control participants showed apparent telomere shortening. One possible interpretation is that openness to ones' ongoing experience in a supportive retreat environment may be important for promoting telomere-related benefits, whereas openness to diverse experiences outside of retreat may lead to engagement in both beneficial and health-compromising behaviors.

### 4.5. Conclusions, limitations, and suggestions for future research

Within the Western Insight tradition, residential retreats are used to facilitate periods of concentrated meditation practice (Goldstein and Kornfield, 2001). Our results support the supposition that intensive practice within a supportive environment—under the guidance of experienced teachers and while removed from the usual demands of daily life—may have important implications for psychological and cellular health. The present findings further suggest that individual differences in personality traits may enhance or mitigate some of the cellular benefits of attending retreat. Nevertheless, there are two notable limitations to our study design: lack of group randomization and use a passive control condition. There are inherent challenges in creating randomized, active control interventions for month-long residential interventions that are structurally comparable in duration, location, diet, teachers, social components, and other potentially contributing factors. We further acknowledge that attending a 1-month residential retreat at a Buddhist-based meditation center is not feasible or appropriate for everyone, limiting the generalizability of our results. For these reasons, we opted to recruit a comparison group designed to minimize discrepancies in meditation experience, expectations, and motivations between groups. Indeed, groups were matched on a number of lifestyle and behavioral-health relevant factors (see Supplemental Materials).

As the present study was not designed to disambiguate the effects of formal meditation practice from the retreat intervention as a whole, it is important to consider our results in tandem with shorter interventions employing more targeted controls, such as Epel et al. (2016), who utilized a vacation control condition to account for the biological consequences of removal from daily life stressors. Although we attribute our results to the retreat intervention overall, the relations we observed between measures of retreat engagement and telomere biology suggest that formal meditation practice meaningfully relates to measures of cell aging.

As TL varies by cell type, one potential confound that warrants further investigation is the possibility that immune cell distributions may have shifted between assessments. We measured TL in PBMCs, which consist of many different cell types, including monocytes and lymphocytes (T-cells—such as CD8 and CD4 cells, B-cells, and natural killer cells). Lymphocyte redistribution, which can occur temporarily in response to acute stress (Dhabhar, 2011; Dhabhar et al., 2012; Rosenberger et al., 2009) may lead to "pseudo-lengthening," whereby average TL measurements increase due to an increase in cell types having longer telomeres (Epel, 2012). It is possible that meditation training may have reduced retreat participants' stress reactivity, thereby minimizing stress-related cell redistribution during the post-assessment blood collection. However, we sought to minimize the influence of acute stress responses for controls in our protocol by incorporating a period of meditation prior to the blood draw. It is also possible that the retreat intervention reduced overall psychological stress profiles, thereby shifting cell populations in a more lasting manner, as MBSR has been shown to increase or maintain CD4+T cells in HIV patients (Creswell et al., 2009; SeyedAlinaghi et al., 2012). There are many ways that changes in cell types could produce a pattern of telomere elongation, and because we did not (and the field cannot yet) measure per-cell telomere length changes, we label the phenomenon here "apparent telomere lengthening," and await further evidence of true per cell telomere lengthening in humans. However, the pattern of gene expression changes observed in the present study also bolsters the conclusion that the retreat-related telomere increases are attributable to actual, versus pseudo, lengthening—though future studies using flow cytometry to assess cell distributions will be necessary to disambiguate these alternatives.

In sum, we report that meditation practice in a retreat context may have salutary effects on telomere regulation, which appear sensitive to individual differences in personality. As this is the first intervention to demonstrate an apparent increase in telomere length in such a short timeframe, this finding should be interpreted both with enthusiasm and caution. Future work will be needed to replicate these relatively short-term effects and to determine whether increases in telomere length persist once practitioners resume their typical daily lives and normative social engagement. We also found provocative relationships between telomerase activity and measures of retreat engagement and prior meditation experience, and propose an explanatory framework that might reconcile these and other telomerase findings in the meditation research literature. Finally, we demonstrated the utility of assessing multiple measures of telomere biology and statistically modeling sources of variability in TL telomere length assays.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bbi.2018.03.003.

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