Psychoneuroendocrinology (2010) xxx, xxx–xxx

available at www.sciencedirect.com

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Intensive meditation training, immune cell telomerase activity, and psychological mediators

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Received 22 January 2010; received in revised form 28 August 2010; accepted 17 September 2010

KEYWORDS
Meditation;
Neuroticism;
Perceived control;
Purpose in life;
Stress;
Telomerase

Summary
Background: Telomerase activity is a predictor of long-term cellular viability, which decreases with chronic psychological distress (Epel et al., 2004). Buddhist traditions claim that meditation decreases psychological distress and promotes well-being (e.g., Dalai Lama and Cutler, 2009). Therefore, we investigated the effects of a 3-month meditation retreat on telomerase activity and two major contributors to the experience of stress: Perceived Control (associated with decreased stress) and Neuroticism (associated with increased subjective distress). We used mediation models to test whether changes in Perceived Control and Neuroticism explained meditation retreat effects on telomerase activity. In addition, we investigated whether two qualities developed by meditative practice, increased Mindfulness and Purpose in Life, accounted for retreat-related changes in the two stress-related variables and in telomerase activity.
Methods: Retreat participants (n = 30) meditated for ~6 h daily for 3 months and were compared with a wait-list control group (n = 30) matched for age, sex, body mass index, and prior meditation experience. Retreat participants received instruction in concentrative meditation techniques and complementary practices used to cultivate benevolent states of mind (Wallace, 2006). Psychological measures were assessed pre- and post-retreat. Peripheral blood mononuclear cell samples

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0306-4530/$ – see front matter
doi:10.1016/j.psyneuen.2010.09.010

were collected post-retreat for telomerase activity. Because there were clear, a priori hypotheses, 1-tailed significance criteria were used throughout.
Results: Telomerase activity was significantly greater in retreat participants than in controls at the end of the retreat ($p < 0.05$). Increases in Perceived Control, decreases in Neuroticism, and increases in both Mindfulness and Purpose in Life were greater in the retreat group ($p < 0.01$). Mediation analyses indicated that the effect of the retreat on telomerase was mediated by increased Perceived Control and decreased Neuroticism. In turn, changes in Perceived Control and Neuroticism were both partially mediated by increased Mindfulness and Purpose in Life. Additionally, increases in Purpose in Life directly mediated the telomerase group difference, whereas increases in Mindfulness did not.
Conclusions: This is the first study to link meditation and positive psychological change with telomerase activity. Although we did not measure baseline telomerase activity, the data suggest that increases in perceived control and decreases in negative affectivity contributed to an increase in telomerase activity, with implications for telomere length and immune cell longevity. Further, Purpose in Life is influenced by meditative practice and directly affects both perceived control and negative emotionality, affecting telomerase activity directly as well as indirectly.

1. Introduction

1.1. Telomerase: linking stress with physical health

Although relations between psychological functioning and physical health have long been documented, mechanistic links are only beginning to be understood at the cellular level (e.g., Miller et al., 2009). Telomere length has recently been proposed as a useful 'psychobiomarker' linking stress and disease (Epel, 2009). Shortened telomere length and reduced telomerase (the cellular enzyme primarily responsible for telomere length and maintenance) predict a host of health risks and diseases (Blackburn, 2000; Serrano and Andres, 2004; Lin et al., 2009b), and new findings suggest they may be regulated in part by psychological stress, stress appraisals, and well-being (Epel et al., 2004, 2009a; Ornish et al., 2008). The literature on Buddhist traditions has long suggested that meditation can reduce psychological stress and enhance well-being (e.g., Dalai Lama and Cutler, 2009). In the present study, we investigated whether meditative practice is associated with immune cell telomerase activity and whether this association is at least partly explained by changes in two major contributors to the experience of stress: Perceived Control and Neuroticism (see Fig. 1).

Telomeres are protective DNA sequences at the ends of chromosomes that ensure genomic stability during cellular replication, but they shorten with each cell division and additionally shorten under conditions of oxidative stress unless counteracted by telomerase action (Blackburn, 1991). Below a critical telomere length, cell division can no longer occur and a cell is at a higher risk for entering a state of senescence, which may underlie tissue aging (Fossel, 2000; Chan and Blackburn, 2004). During human aging, as cells divide, telomere length decreases on average and hence is one indicator of a cell's biological age (Frenck and Blackburn, 1998), predicting physical health and longevity (e.g., Cawthon et al., 2003; Epel et al., 2009b; Njajou et al., 2009). Although cross-sectional studies show that telomere length decreases with age (on average), recent longitudinal studies

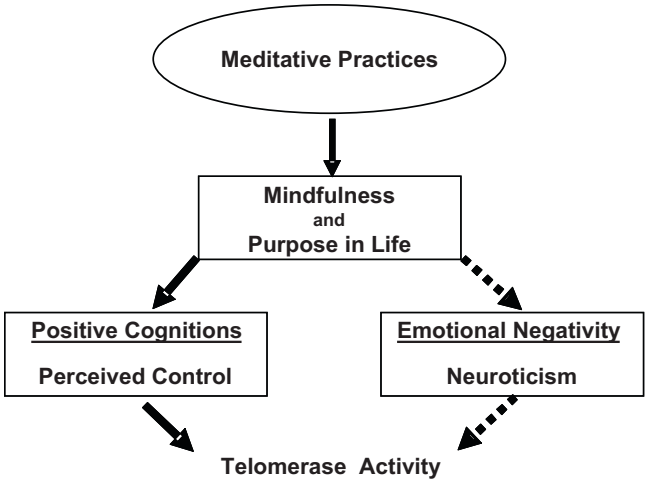

Figure 1 A schematic depiction of how meditation practice might influence telomerase activity by increasing perceived control and decreasing neuroticism (figure adapted from Epel et al., 2009a). Solid and dashed arrows depict positive and inverse relations, respectively.

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indicate that in a significant fraction of people, peripheral blood mononuclear cell telomere length can increase over time (Epel et al., 2009b; Nordfjäll et al., 2009; Farzaneh-Far et al., 2010). This latter finding opens the door for determining potential malleable regulators of the rate of telomere length shortening. The rate of telomere shortening or lengthening depends on multiple factors including activity levels of the enzyme telomerase (Blackburn, 2000), which has the notable capacity to add DNA sequences back to telomeres, actively increasing their length and preserving healthy cell function (e.g., Kim et al., 2003).

Immune cell telomerase activity may play a role in mediating the relation between psychological stress and disease. Greater perceived stress, greater negative affect, and a number of stress-related cardiovascular risk factors (e.g., higher resting heart rate, elevated levels of stress hormones) are associated with lower telomerase activity (Epel et al., 2004, 2006). Moreover, individuals who respond to an acute stressor with suppressed vagal tone, which is an autonomic response that is inversely associated with negative affect and vulnerability to psychological stressors (Porges, 1995; Carney et al., 2001), also show lower telomerase activity, indicating a relation with psychological and physiological stress (Epel et al., 2006).

1.2. Perceived control and neuroticism as potential variables affecting telomerase activity during a meditation retreat

Given the relation between perceived stress and telomerase activity (Epel et al., 2004) and the literature on Buddhist traditions suggesting that meditation reduces psychological stress (Dalai Lama and Cutler, 2009), we reasoned that the specific psychological variables affecting immune cell telomerase activity during a meditation retreat might be the same ones that underlie individual differences in experienced stress. The great variation among individuals in experienced stress can be accounted for in part by other variables, including a feeling of inadequate control and the general propensity for negative affectivity, labeled neuroticism in personality studies. For example, a feeling of inadequate control has been associated in both classic and contemporary studies of animals and humans with greater psychological stress and less adaptive responses to stressful events (e.g., Seligman, 1972; Averill, 1973; Wallston et al., 1987; Vollmayr and Henn, 2001; Mausbach et al., 2006, 2008; Abelson et al., 2008; Karmilovich, 2009). Internal locus of control influences responses to stressful events by improving coping strategies (e.g., Krause and Stryker, 1984; Litt, 1988) and reducing anxiety (e.g., Chorpita and Barlow, 1998). Thus, perceived control is a key marker of stress resilience. Another contributor to stress is trait negative affectivity or neuroticism (chronically and characteristically feeling tense, anxious, moody, or insecure). High trait neuroticism typically amplifies stress responses in humans, particularly to acute stressors (Brody et al., 1996; Schneider, 2004; Shurgot and Knight, 2005), which leads to "greater stress vulnerability" (Suls, 2001).

Here, we explore the possibility that perceived control and neuroticism affect immune cell telomerase activity. Several physiological arousal processes may underlie relations between between perceived control and neuroticism with telomerase; they have been reviewed elsewhere (Epel et al., 2009a) and are not considered here.

1.3. Meditation practice as a potential regulator of perceived control and neuroticism

Increases in perceived control and decreases in neuroticism are plausible effects of meditative practice (e.g., Wallace and Shapiro, 2006). However, studies examining the effect of meditative practice on stress or well-being often raise methodological or interpretive questions. For example, self-selection into meditation training can result in a biased sample: Although lower neuroticism scores are reported by QiGong meditators who have practiced for a greater number of years (Leung and Singhal, 2004), meditation training is more likely to be discontinued by people with higher trait neuroticism (Delmonte and Kenny, 1985; Delmonte, 1988). Moreover, attributing outcomes to meditation per se can be tenuous, because it is often difficult to create an ideal control condition. One way to begin to handle such issues is to assess changes in measurable qualities that are specifically developed by meditative practice and determine whether they account, in a controlled, longitudinal study, for other positive outcomes.

One aspect of meditative practice is mindfulness, which is broadly defined in Buddhist traditions as the ability to maintain attention toward chosen meditative objects (Wallace, 2005) and also includes an emphasis on attending to beneficial thoughts (Gethin, 2001). Although Western concepts of mindfulness draw on these Buddhist views, they often diverge from this traditional understanding (Grossman, 2008; Wallace, 2008). Mindfulness is operationalized in contemporary psychological models as a multifaceted construct tapped, in part, by self-report measures of abilities to carefully observe and label internal or external experience in a non-reactive, non-judgmental manner (Baer et al., 2006). Studies have shown that this type of naturally occurring, dispositional mindfulness is inversely related to neuroticism (for a meta-analysis, see Giluk, 2009) and positively related to other forms of self-regulation and to positive emotions (e.g., Brown and Ryan, 2003). Mindfulness may be developed in practices that maintain attention on a meditative object (e.g., one's breath, awareness itself, actions and sensations of daily activity; see Wallace, 2006). Mindfulness-based training has been widely reported to improve psychological and physical well-being and to reduce stress (for reviews, see Grossman et al., 2004; Chambers et al., 2009; Rubia, 2009). However, aside from more recent exceptions (e.g., Baer et al., 2008; Carmody and Baer, 2008; Shapiro et al., 2008), most of these mindfulness training studies have considered mindfulness as an outcome measure along with other outcomes, rather than as a quality developed during a wider meditative practice that explains other positive results. Moreover, its effect on telomerase has never been assessed. Here, we test whether mindfulness mediates the effects of meditative practice on perceived control, neuroticism, and telomerase activity. We assign mindfulness this mediating role because it is an explicit target of meditation practice (Wallace, 2006), which is expected to bring about beneficial outcomes, such as better emotion regulation and greater emotional stability (e.g., Bishop et al., 2004; Brown and Ryan, 2003). Moreover, previous theoretical and empirical contributions to research on mindfulness have emphasized the causal role of mindfulness practices. They (e.g., Borders

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et al., 2010) have pointed out that such practices reduce negative rumination (which contributes to depression). In addition, a recent study assigned mindfulness a causal role in a model of positive reappraisal processes that contribute to adaptive coping (Garland et al., 2009; for review see Garland et al., 2010).

Mindfulness is only one quality cultivated by meditative practice and other qualities have only recently begun to be explored (e.g., Kraus and Sears, 2009; Sahdra et al., 2009). One understudied quality developed during meditative practice is a shift in intentions and priorities away from hedonic pleasure or superficial well-being (Nanamoli and Bodhi, 1995; Wallace and Shapiro, 2006), making one's deeper "purpose in life" (a measurable psychological construct; Ryff, 1989) clearer. Although meaning in life is a well-established correlate of other measures of psychological well-being (Ryff and Keyes, 1995; Klinger, 1998), it has never been examined as a benefit of meditation practice that might account for other positive outcomes. Here, we consider the possibility that enhanced purpose in life is one of the mediators of the relation between meditation practice and perceived control and negative affectivity and telomerase activity. We assign purpose in life this mediating role based on a recent integrative model of the ways in which the sense of overarching meaning (extending beyond a particular situation) affects health outcomes via changes in specific psychological mediators (e.g., changes in appraisal or coping mechanisms that reduce negative affect) (for a review of this model, see Bower et al., 2008). The causal nature of the relation between meaning-finding and affect is supported by longitudinal studies, which suggest that the ability to create an overarching sense of meaning in the face of stressful events precedes a change in affect (for a meta-analysis, see Helgeson et al., 2006). With respect to meditation, Fredrickson et al. (2008) used causal path analyses and growth modeling to show that the amount of weekly time spent in 'loving-kindness' meditation predicted a cumulative, daily increase in positive emotion over a 2-month period. This increase contributed to an increase in life satisfaction and reduced depressive symptoms *via* the mediation of purpose in life and mindfulness.

1.4. The present study and hypotheses

Using a longitudinal wait-list controlled design, we determined whether participation in an intensive 3-month meditation retreat would result in increased mindfulness, an enhanced sense of purpose in life, greater perceived control, decreased neuroticism, and greater post-retreat immune cell telomerase activity. Mediation models were used to test two sets of predictions, based on the framework in Fig. 1. First, we tested whether the meditation-related changes in post-retreat telomerase activity were mediated by any of the four measured psychological variables. Second, we tested whether retreat-related changes in indicators of positive cognitions and emotional negativity (i.e., increases in perceived control and decreases in neuroticism) were mediated by changes in either mindfulness or purpose in life.

We made and tested a number of predictions about the associations between meditation training, psychological change, and telomerase activity: (1) The retreat group (compared to the matched control group) would exhibit greater post-retreat telomerase activity and show increases in mindfulness, purpose in life, and perceived control and larger decreases in neuroticism. (2) Group differences in post-retreat telomerase activity would be mediated by meditation-influenced increases in mindfulness, purpose in life, and perceived control, and decreases in neuroticism. (3) Meditation-induced increases in mindfulness and purpose in life would mediate retreat-related increases in perceived control and decreases in neuroticism.

2. Materials and methods

2.1. Study overview

Sixty men and women (aged 21—69) were matched on demographic variables and meditation experience (described below) and randomly assigned to either an on-site, three-month meditation retreat or a wait-list control group. All participants were assessed before and after the retreat with self-report measures (details below), and telomerase activity was assessed in both groups in peripheral blood mononuclear cells (PBMC) obtained at the end of the retreat. Self-report measures were also administered in a subsequent follow-up. All samples and self-report measures were collected at the site of the retreat.

2.2. Participants

Participants were recruited nationally through advertisements displayed in meditation centers and Buddhist magazines and on Buddhist websites. The ad stated that the study's primary aim was to "investigate the relation between meditation and well-being." Interested individuals submitted applications and were screened (with a 50% acceptance rate) based on the following criteria: (1) age between 21 and 70; (2) an agreement to refrain from alcohol, tobacco, and recreational drug use during the retreat and from tobacco and recreational drug use in the 3 months prior; (3) availability at all testing points and the flexibility to be assigned to either the wait-list control group or the retreat group; (4) no serious medical or psychological problems; axis I psychiatric impairments were assessed by administering both the M.I.N.I. screen (Sheehan et al., 1998) and a brief clinical telephone interview, conducted by a licensed clinical psychologist; (5) previous participation in three or more short (5—10 day) meditation retreats, with at least one of them led by Alan Wallace, Ph.D., who led the retreat in this study. This last criterion ensured that participants knew what the retreat would entail and were unlikely to leave the study prematurely.

Stratified matched assignment was used to assign participants to either the retreat condition (n = 30) or the waitlist control condition (n = 30), with groups matched on sex (28 men and 32 women), age (M = 48, range 22—69), and years of self-reported meditation experience (M = 13) (Table 1).

Control participants were flown to the retreat center before, during, and after the retreat to be assessed on multiple measures along with retreat participants, and they were on-site for 5 days prior to PBMC sample collection to adjust to the setting and altitude. Otherwise, the controls spent the remainder of the retreat period at their own

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Table 1 Group Matching: Demographics and Psychological Variables.

	Control	Retreat	*t*	*p*[j]
All Participants[a]				
General				
Age[c]	46 (22–65)	49 (23–69)	0.79	n.s
Sex	14 M, 16 F	14 M, 16 F	–	–
Education[d]	4.9 (3–6)	5.2 (1–6)	1.09	n.s
Income[e]	6.5 (1–11)	6.9 (1–11)	0.41	n.s
BMI[f]	23.6 (17.7–39.5)	23.7 (19.3–32.9)	0.34	n.s
Meditation Experience				
Retreats[g]	15 (2–100)	13 (2–50)	0.67	n.s
Daily[h]	54 (13–155)	56 (9–180)	0.18	n.s
Lifetime[i]	2,668 (200–15,000)	2,549 (250–9,500)	0.16	n.s
Sub-sample[b]				
General				
Age[c]	50 (22–65)	53 (24–67)	0.59	n.s
Sex	12 M, 13 F	10 M, 6 F	–	–
Education[d]	4.8 (3–6)	5.2 (1–6)	1.02	n.s
Income[e]	7.3 (1–11)	7.1 (1–11)	0.34	n.s
BMI[f]	23.1 (17.7–27.4)	22.9 (19.3–30.5)	0.06	n.s
Meditation Experience				
Retreats[g]	16 (2–100)	14 (2–50)	0.92	n.s
Daily[h]	55 (13–155)	52 (9–90)	0.19	n.s
Lifetime[i]	2,979 (200–15,000)	2,588 (400–8,720)	0.86	n.s

[a] All participants that participated in the study.
[b] Sub-sample of participants for which telomerase activity could be assessed.
[c] Age in years at the beginning of participation in the study.
[d] Scale of education achievement (1 = less than high school; 2 = high school degree; 3 = some college; 4 = college degree; 5 = some graduate; 6 = graduate degree).
[e] Income category (1 = under 10K, 2 = 10–20K, 3 = 20–30K, 4 = 30–40K, 5 = 40–50K, 6 = 50–60K, 7 = 60–70K, 8 = 70–80K, 9 = 80–90K, 10 = 90–100K, 11 = over 100).
[f] Body Mass Index (pre–retreat) = mass (lbs) $\times$ 703/height $(\text{in})^2$.
[g] Total number of meditation retreats lasting at least 5 consecutive days. Reports available for 28 wait-list control and 30 retreat participants.
[h] Average daily minutes of formal meditation practice. Reports available for 28 wait-list control and 25 retreat participants.
[i] Total lifetime hours of formal meditation practice. Reports available for 30 wait-list control and 29 retreat participants.
[j] $p > .2$ for all tests using one-tailed significance criteria for all.

homes, living their usual daily lives. Retreat participants paid for their room and board during the retreat (~$5300), but were compensated for participation in our assessments at the rate of $20/h. Control participants were also compensated for their participation in assessments and additionally for travel to the retreat site. All procedures were approved by the institutional review board of the University of California, Davis and carried out with written consent and adequate understanding by all participants using a protocol.

2.3. Meditation training

The meditation retreat took place within an isolated retreat setting (the Shambhala Mountain Center in northern Colorado), where retreat participants lived and practiced meditation techniques for 3 months. They were instructed in these practices by Alan Wallace, Ph.D., a well-known Buddhist scholar and practitioner, who has described the practices used for this particular study in detail (Wallace, 2006). These practices can be broadly categorized as the cultivation of attentional skills and the generation of benevolent mental states.

Attentional skill practices involve focusing the mind. The mind is first calmed to reduce distraction (the practice of *mindfulness of breathing*), and then the meditator, within that calmness, is trained to be aware of moment-to-moment thoughts in a manner that is non-reactive and stable yet discerning and vivid (the practice of *observing mental events* or "settling the mind in its natural state"). Further, the nature of consciousness is sometimes explored by disengaging attention from one's thoughts and focusing on awareness itself as the object of concentration (using the practice of *observing the nature of consciousness* or "awareness of awareness").

Generating benevolent mental states involves the following: Loving-kindness practices arouse a heartfelt wish that self and others may experience happiness and its true causes, which serves as an antidote for malice. *Compassion* practices arouse a heartfelt wish that self and others may be free from suffering and its true causes, which is intended to serve as an antidote for cruelty. Practices intended to increase *empathetic joy* arouse delight in one's own and other people's joys and virtues, which serves as an antidote for envy and cynicism. Finally, *equanimity* practices arouse an impartial and

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unconditional sense of affectionate concern for others, regardless of their relation to oneself, which serves as an antidote to self-centered attachment and aversion.

The meditation training group met with Dr. Wallace in the mornings and evenings for short guided meditations and discussions. For the remainder of the day, participants engaged in solitary meditation sessions, for an average of 6.3 h in total (*SD* = 1.34). Although the main focus of the retreat was the cultivation of attentional skills, with the generation of benevolent states playing an ancillary role, retreat participants were encouraged to explore all of the methods presented. Most of them then settled on two or three of the practices. Participants recorded the type and duration of meditation practice in daily logs. At a follow-up assessment, participants also estimated the amount of time they had devoted to any type of Shamatha practice since the end of the retreat (~5 months).

When participants were not engaging in the practices specified above, they were instructed to maintain peripheral attention on a chosen meditative object while being mindful of actions and sensations involved in daily activities such as walking and eating. Participants also met individually with Alan Wallace on a weekly basis for clarification or guidance.

2.4. Telomerase measurement

2.4.1. Blood sample collection, PBMC isolation, and extract preparation

For each participant, 10 ml of peripheral blood was collected and anticoagulated in BD Vacutainer® CPT tubes with density gradient polymer gel and sodium citrate additives. The PBMC fraction was isolated from each blood sample using density gradient centrifugation (3500 rpm, 20 min, 18–25 °C). Immediately following centrifugation, the PBMC layer was collected. Cells were then washed 3 times in phosphate-buffered saline (PBS) by centrifugation at 3750 rpm for 10 min at room temperature. Cells were re-suspended in PBS and live cells were counted with Trypan blue staining solution using 5 squares of a hemocytometer, each measuring 0.04 mm^2. Using this cell count, 6.25 million PBMCs were pelleted and extracts corresponding to 31,250 cells/μL were made, based on the protocol provided in the TRAPeze telomerase detection kit (Chemicon, Temecula, CA). The extracts were stored at −80 °C until use.

2.4.2. Telomeric repeat amplification protocol

Quantification of telomerase activity was measured from the extract using the telomeric repeat amplification protocol (TRAP) as previously described (Kim and Wu, 1997) with a commercial kit (TRAPeze®, Chemicon, Temecula, CA). Between 15,625 and 31,250 cells were used for TRAP reactions to ensure that the assay was in linear range for each sample (Lin et al., 2009a). The reaction was carried out according to the TRAPeze kit manual. The PCR program used was: 94 °C for 2 min; 94 °C for 30 s, 59 °C for 30 s for 30 cycles. The products were fractionated on a 10% polyacrylamide-8 M urea sequencing gel. The gel was exposed to a phosphorimager plate overnight and scanned on a STORM 860 molecular imager (GE Healthcare, Piscataway, NJ). The 293T cell line was used as a positive telomerase activity control and reference standard.

Telomerase activity was quantified using the software ImageQuant 5.2 (GE Healthcare, Piscataway, NJ). Signals from the product ladders on the gels were added and normalized against the signal from an internal control band for the same lane to get the product/internal control value. For each telomerase activity assay reaction, the product/internal value was divided by the product/internal control value from twenty 293T cells and then multiplied by 20 to obtain the final telomerase activity units, defined as 1 unit = the amount of product from one 293T cell/15,625 PBMCs. The inter-assay variability (CV) was 6.7%. After obtaining values of telomerase activity for 15,625 cells, a linear correction was applied whereby values were multiplied by 0.64 so that results were comparable with previous findings, which typically report activity per 10,000 cells.

2.4.3. Criteria for assessing telomerase activity

Within the groups of retreat and control participants, eligibility for telomerase activity assessment included (1) consent to have a blood sample drawn; (2) an adequate number of peripheral blood mononuclear cells (PBMCs) from the pre-processed blood sample; (3) no self-reported illness on the day of (or surrounding) blood sample collection; (4) no self-reported, preexisting health conditions; (5) a body mass index (BMI) that did not indicate morbid obesity (BMI above 40); (6) no use of medications that could potentially affect telomerase activity derived from PBMCs.

Fourteen participants either declined to have their blood drawn (2 participants) or their blood samples contained inadequate numbers of PBMCs (12 participants), reducing the assayed sample size to 26 controls and 20 retreat participants. Of the assayed samples, one participant in the control group had a BMI > 40, indicating morbid obesity. Within the retreat group, one participant reported taking fertility treatments during the study, one reported a liver disorder, and one reported cancer remission and was taken to a medical facility during the retreat for an unrelated stomach ulcer. This reduced sample sizes *for models that included telomerase* in the retreat group (to $n = 17$) and control group (to $n = 25$). Within this reduced sample, demographic variables and prior meditation experience did not differ significantly between retreat and control groups (Table 1). Additionally, within the treatment group, the group of participants who were not included in the analyses did not significantly differ from the remaining 17 subjects on any of the pre-treatment baseline assessments. That is, independent sample *t*-tests comparing the included vs. excluded participants were not significant for pre-retreat Purpose in Life ($t = 0.14$, $p = 0.89$, two-tailed), Mindfulness ($t = 1.30$ $p = 0.27$, two-tailed), Neuroticism ($t = -0.71$, $p = 0.49$, two-tailed), or Perceived Control ($t = 1.61$, $p = 0.12$, two-tailed) (Although not significant, the mean value for pre-retreat Perceived Control was slightly lower in the group that was not included in the analyses.).

2.5. Psychological measures

Psychological assessments were completed at pre and post-retreat time-points. At the post-retreat time-point, assessments were completed within 2 days prior to blood sample collection. Follow-up at home psychological assessments were completed for the retreat group at ~5 months following the retreat. All measures contained items that were rated on

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Table 2 Partial correlations between psychological measures in the combined control and retreat groups (controlling for age).

Pre-retreat	α	Mindfulness	Purpose	Control
Mindfulness	0.95[a]	—		
Purpose	0.74	0.29*	—	
Control	0.87	0.41**	0.62	—
Neuroticism	0.86	−0.48***	−0.44***	−0.68***

Δ(Post − pre)	ΔMindfulness	ΔPurpose	ΔControl
Mindfulness	—		
Purpose	0.25*	—	
Control	0.37**	0.55***	—
Neuroticism	−0.42**	−0.35**	−0.49***

α = Cronbach's alpha at pre-retreat.
[a] Entire scale averaged (individual facets ranged from 0.80 to 0.93).
* $p < 0.05$ (all one-tailed criteria).
** $p < 0.01$ (all one-tailed criteria).
*** $p < 0.001$ (all one-tailed criteria).

a 7-point scale, ranging from 1 (*Disagree Strongly*) to 7 (*Agree Strongly*). Two participants did not complete any of the pre-retreat psychological assessments, and an additional two did not complete the Mindfulness measure. One participant did not complete any of the follow-up assessments and an additional participant completed all follow-up assessments except the Mindfulness measure. These participants were not included in analyses involving those measures. The internal reliability indices (Cronbach's alpha) of the measures and their intercorrelations are reported in Table 2.

2.5.1. Mindfulness

Participants completed the 37-item Five Facet Mindfulness Questionnaire (FFMQ), which assesses five facets of Mindfulness (observing or noticing experience; acting with attentional awareness or avoiding automatic pilot; non-reactivity to internal experience; describing or labeling feelings; non-judging of experience) (Baer et al., 2006). The facets of the FFMQ were intercorrelated, and a factor analysis indicated that a single factor accounted for 55% of the variance in the facet scores, which loaded on the factor with values ranging from 0.65 to 0.84. We therefore used a single score for mindfulness, the mean of all the item scores.

2.5.2. Purpose in life and perceived control

Ryff's (1989) Well-Being Scale assesses how a person rates various aspects of his or her functioning on six dimensions, one of which is Purpose in Life and another of which is Environmental Mastery (or, in our terms, Perceived Control). We used the 9-item Purpose in Life subscale to assess changes in a person's sense that life is meaningful, organized around clear aims, and clearly directed. We used the 9-item Environmental Mastery subscale to measure Perceived Control over situations and circumstances.

2.5.3. Neuroticism

The Big Five Inventory (John et al., 1991; John and Srivastava, 1999) is a simple measure of the five major broadband personality factors derived from intensive study of personality structure over the past few decades. We used the 8-item Neuroticism scale to assess dispositional negative emotionality. Higher scores indicate being relatively tense, moody, and anxious.

3. Statistical approach and predictions

3.1. Procedures

For analyses involving psychological variables, age was included as a covariate. For analyses involving telomerase, both age and post-retreat BMI were included as covariates. The analyses included multiple steps. First, standard ANCOVA and post hoc *t*-tests were used to identify significant retreat vs. control differences on the measures. The effect of retreat participation on post-retreat telomerase activity was assessed using ANCOVA, with Group (retreat vs. control) as a between-subjects variable and age and post-retreat BMI as covariates. The effects of retreat participation on changes in Mindfulness, Purpose in Life, Perceived Control, Neuroticism, and BMI were assessed using ANCOVA, with Time (pre- and post-retreat) as a within-subjects variable, Group (retreat vs. control) as a between-subjects variable, and age as a covariate. Preliminary correlations were used to examine relations among psychological measures and to assess associations between baseline psychological function and retreat-related effects.

Second, regression-based mediation analyses were used to determine whether changes in any of the psychological measures mediated group differences in telomerase activity and, further, whether retreat-related changes in Mindfulness or Purpose in Life mediated group differences in changes in Perceived Control or Neuroticism. Regression-based mediation procedures were performed using the product-of-coefficients method (Sobel, 1982, 1986), and mediating effects were derived using the recommended bootstrapping procedures (MacKinnon et al., 2000, 2004; Preacher and Hayes, 2004; MacKinnon and Fairchild, 2009; Hayes, 2009).

More specifically, a regression coefficient (and associated *t*-test) was first calculated for the effect of the independent variable on the mediating variable (path a), the mediating variable on the dependent variable (path b), the independent variable on the dependent variable without the inclusion of mediators (path c), and the independent variable on the dependent variable after the mediator was included (path c′). Then, the product-of-coefficients (paths a*b) was calculated to give a point estimate for the indirect (mediating) effect. This indirect, mediating effect was derived using a bootstrapping procedure.

Bootstrapping is an accepted, non-parametric resampling technique that can be used to derive summary statistics for a given sample (e.g., Efron and Tibshirani, 1993). It is a useful method to use when data are not normally distributed, as is usually the case for small sample sizes. And, it has recently been recommended for regression-based mediation, because indirect, mediating effects (paths a*b) are only normally distributed in very large samples (MacKinnon et al., 2000, 2004; Preacher and Hayes, 2004; MacKinnon and Fairchild, 2009; Hayes, 2009).

The bootstrapping procedure involves randomly sampling (with replacement) a subset of the data and calculating a

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statistic of interest. This is repeated thousands of times to give a sampling distribution for that statistic. Then, the statistic of interest is derived from this sampling distribution. In the present study, the indirect, mediating effect within a given mediation model (i.e., the product of coefficients, paths a*b) was calculated 5000 times (using random sampling with replacement) to build a sampling distribution. Then, the point estimate for the indirect effect was derived from this (more normally shaped) sampling distribution and the corresponding confidence intervals for this estimate were also determined from this distribution. These confidence intervals are bias-corrected and accelerated (*BCa*), correcting for skew and median bias (Efron and Tibshirani, 1993). Point estimates of mediated effects are interpreted as significant if zero is not contained within the confidence intervals (Preacher and Hayes, 2004). This use of bootstrapping is recommended, over the standard product-of-coefficients method (i.e., Sobel, 1986), because indirect effects are almost never normally distributed, except in very large samples (MacKinnon et al., 2000, 2004; Preacher and Hayes, 2004; MacKinnon and Fairchild, 2009; Hayes, 2009). The proportion of the mediated effect is reported as the indirect (mediated effect)/total effect.[1]

All analyses were performed with SPSS using non-centered variables. Simple mediation analyses were performed using the INDIRECT SPSS macro (version 4; Preacher and Hayes, 2004). Due to unidirectional, a priori hypotheses, 1-tailed tests of significance and 90% *BCa* were used in all analyses.

4. Results

4.1. Sample description

The majority of participants (67%) held advanced degrees or had some graduate or professional training, with the remainder having some college education or holding a college degree (31%) or having less than a high school education (2%). The median annual income category was $60,000–70,000. Fewer than half of the participants were married (41%), with the remaining single (19%), dating (15%), divorced (12%), cohabitating (6%), engaged (5%), or widowed (2%). Sixty-four percent were European American, 14% European, 12% Hispanic, 4% of mixed ethnicity, and 3% Asian American. Seventy percent of participants resided in the United States, with the remaining 30% residing in Canada, Mexico, and various countries in Europe and Asia. There were no differences between groups in these sociodemographic variables (Table 1).

Body mass index was significantly reduced in retreat participants from pre to post-retreat. That is, there was a significant Group x Time interaction [$F(1,53) = 7.52$, $p < 0.01$, two-tailed], and the same trend was noted in the subsample in which telomerase was assessed [$F(1,34) = 3.79$, $p = 0.06$, two-tailed]. Although BMI did not differ between groups at pre- or post-retreat (Table 3), BMI significantly decreased from pre- to post-retreat in the retreat group ($t = 2.74$, $p < 0.05$, two-tailed), but not in the control group ($t = -1.35$, $p = 0.19$). A similar pattern was noted in the subsample of participants in which telomerase was assayed, where BMI significantly decreased in the retreat group ($t = 2.52$, $p < 0.05$, two-tailed) but not in the control group ($t = -0.60$, $p = 0.56$).

Table 3 Means (SD) for psychological variables and BMI at pre and post-retreat.

	Control[c]	Retreat[d]	*t*-value
Pre-retreat			
All Participants[a]			
Mindfulness	4.92 (0.88)	5.36 (0.69)	2.14*
Purpose	5.48 (0.80)	5.59 (0.83)	0.49
Control	5.20 (1.04)	5.32 (1.04)	0.41
Neuroticism	3.35 (1.01)	3.26 (1.14)	0.04
Body Mass Index	23.62 (4.33)	23.66 (3.37)	0.03
Sub-Sample[b]			
Mindfulness	4.92 (0.93)	5.49 (0.50)	2.24*
Purpose	5.62 (0.75)	5.61 (0.70)	0.06
Control	5.43 (0.93)	5.58 (1.05)	0.48
Neuroticism	3.19 (1.04)	3.13 (1.29)	0.16
Body Mass Index	23.06 (2.56)	22.95 (2.95)	0.13
Post-retreat			
All Participants[a]			
Mindfulness	4.96 (0.77)	5.85 (0.67)	4.78***
Purpose	5.25 (0.77)	5.84 (0.68)	3.16**
Control	5.18 (0.87)	5.81 (0.71)	3.10**
Neuroticism	3.39 (0.94)	2.82 (1.05)	2.22*
Body Mass Index	23.74 (4.70)	23.16 (3.50)	0.59
Sub-Sample[b]			
Mindfulness	5.01 (0.79)	5.86 (0.58)	3.81***
Purpose	5.30 (0.73)	5.84 (0.66)	2.48**
Control	5.32 (0.79)	5.97 (0.72)	2.72**
Neuroticism	3.35 (0.96)	2.69 (1.23)	1.93*
Body Mass Index	23.24 (3.13)	22.53 (2.91)	0.74

[a] All participants that participated in the study.
[b] Sub-sample of participants for which telomerase activity could be assessed.
[c] There were no significant changes between pre and post-retreat in the control group.
[d] See text for statistics regarding pre vs. post-retreat differences in the retreat group.
* $p < .05$ (all one-tailed criteria).
** $p < .01$ (all one-tailed criteria).
*** $p < .001$ (all one-tailed criteria).

[1] Quantifying the proportion of variance explained by a mediating pathway is still a matter of discussion (for brief overview, see Hayes, 2009). While standardized regression coefficients and partial r^2 measures can describe the proportion of variance explained by *components* of a mediation model, neither describes the proportion explained by the mediated effect in its *entirety* (Fairchild and MacKinnon, 2009). The proportion of the mediated effect is often reported as indirect (mediated)/total effect (Sobel, 1982). While this proportion is reported in the present article, it is not a true representation of the proportion of variance explained by the mediator, with no upper or lower bounds and biases occurring in small sample sizes (MacKinnon et al., 2007). Although Fairchild et al. (2009) have recently introduced an effect size that estimates this proportion of variance; it is not yet available for models that contain covariates.

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4.2. Difference of post-retreat telomerase activity between control and retreat groups

In the control group, one outlier was identified as having a telomerase value beyond 2.5 standard deviations of the control group mean and was removed from further analyses. The control and retreat groups were homogeneous with respect to error variance [Levene's test; $F(1,38) = 0.53$, $p = 0.47$)], with normal distributions for the retreat group ($W = 0.94$, $p = 0.40$) and control group ($W = 0.94$, $p = 0.13$).

After controlling for age and post-retreat BMI, there was a significant main effect of retreat group participation [$F(1,36) = 3.01$, $p < 0.05$], with greater telomerase activity in the retreat participants than in the control group (Fig. 2). Partial eta squared $(\eta_p^2) = 0.077$, indicating that being assigned to either the retreat or control group accounted for 7.7% of the variance. This effect is small, using the generally accepted benchmarks for effect size (Cohen, 1992). The effects of the covariates — age [$F(1,36) = 0.02$, $p = 0.90$)] and post-retreat BMI [$F(1,36) = 0.01$, $p = 0.92$)] — were not significant.

4.3. Comparison of psychological changes between groups

Relative to controls, retreat participants reported significantly greater increases in Mindfulness, Purpose in Life, and Perceived Control, and a significantly greater decrease in Neuroticism (Fig. 3). That is, after controlling for age, there was a significant Group × Time interaction affecting Mindfulness [$F(1,53) = 16.97$, $p < 0.0001$], Purpose in Life [$F(1,55) = 10.54$, $p < 0.0001$], Perceived Control [$F(1,55) = 11.83$, $p < 0.0001$], and Neuroticism [$F(1,55) = 9.07$, $p < 0.0001$]. These interactions were driven by changes in the retreat group, with self-reported ratings ($M \pm SD$) significantly increasing from pre- to post-retreat on measures of Mindfulness (5.36 ± 0.69 to 5.85 ± 0.67; $t = -5.30$, $p < 0.0001$), Purpose in Life (5.59 ± 0.83 to 5.84 ± 0.68; $t = -2.31$, $p < 0.05$), Perceived Control (5.32 ± 1.04 to 5.81 ± 0.71; $t = -3.77$, $p < 0.0001$), and significantly decreasing on the measure of Neuroticism (3.26 ± 1.14 to 2.82 ± 1.05, $t = 2.89$, $p < 0.001$). Pre-retreat values did not differ between groups for Purpose in Life, Perceived Control, or Neuroticism, but did differ for Mindfulness, with the retreat group being slightly higher than the controls (Table 3). In contrast to pre-retreat values, post-retreat group differences were different between groups for Purpose in Life, Perceived Control, Neuroticism, and the group difference was more pronounced for Mindfulness (Table 3). The same pattern was observed in the subsample of participants in which telomerase was assayed (Table 3).

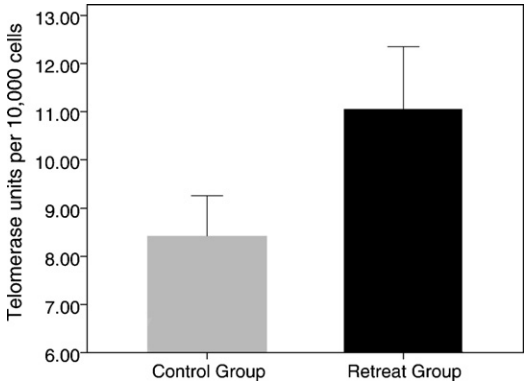

Figure 2 Post-retreat telomerase activity was significantly greater in the retreat group ($p < 0.05$, Error bars: ±1SEM).

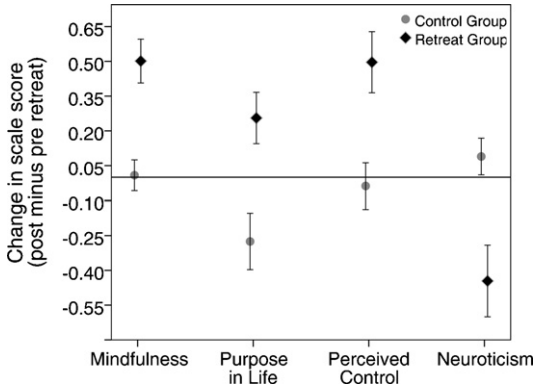

Figure 3 Retreat participants showed increases in Mindfulness and Purpose in Life, along with increased Perceived Control and decreased Neuroticism. The Group (retreat vs. control) × Time (pre- vs. post-retreat) interaction was significant for all measures ($p < 0.0001$. Error bars: ±1SEM). Note: for purposes of comparison across variables, this graph reflects values for subjects who completed all four psychological scales (see methods).

4.4. Changes in psychological variables mediate the group difference in telomerase activity

The values reported below were derived using regression-based mediation analyses procedures. First, regression coefficients were calculated as reported in the path diagrams in Figs. 4 and 6. Then, point estimates for the indirect (mediated) paths and their corresponding confidence intervals were quantified as the product of the regression coefficients (paths a*b), obtained using a bootstrapping procedure, as reported in the text below.

Changes in Mindfulness did not significantly mediate the group effect on post-retreat telomerase (*point estimate* = 0.71; *BCa* = −0.55 to 2.39), with the mediated effect a proportionate 0.34 of the total effect.

Changes in Perceived Control significantly mediated the group effect on post-retreat telomerase activity (Figs. 4B and 5A). That is, the group effect was significantly reduced (path c to path c′) after accounting for changes in Perceived Control (*point estimate* = 1.56, *BCa* = 0.24—3.9), which reduced the group effect to a non-significant relation ($t = 0.70$, $p = 0.25$). A proportionate 0.60 of the total effect (Fig. 4A) was explained by this indirect mediation. The positive point estimate indicates that the more a participant's sense of perceived control increased, the higher his or her level of post-retreat telomerase activity.

Similarly, changes in Neuroticism significantly mediated the group effect on telomerase (Figs. 4C and 5B). That is, the group effect was significantly reduced after accounting for changes in Neuroticism (*point estimate* = 1.5, *BCa* = 0.29—3.8), which reduced the group effect to a non-significant relation ($t = 1.53$, $p = 0.23$). A proportionate 0.57 of the total effect was explained by indirect effects. The positive point estimate

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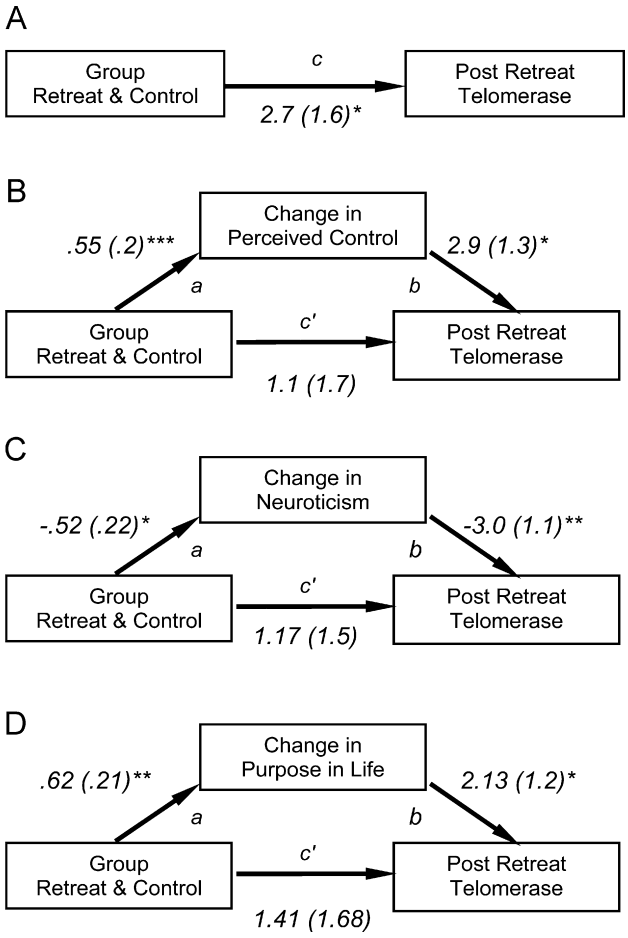

Figure 4 Changes in Perceived Control, Neuroticism, and Purpose in Life significantly mediated the group difference in telomerase activity. Path values are unstandardized regression coefficients with standard errors in parentheses. Please see the text for *t*-test values that correspond to these regression coefficients. The following point estimates represent the mediated (indirect) effects derived from the (bootstrapped) product of paths a and b. (A) Group significantly predicted post-retreat telomerase. (B) Changes in Perceived Control significantly mediated the effects of group on telomerase ($n = 38$, *point estimate* = 1.56; *BCa* = 0.24—3.9). (C) Changes in Neuroticism significantly mediated the effects of group on telomerase ($n = 38$, *point estimate* = 1.50; *BCa* = 0.29—3.8). (D) Changes in Purpose in Life significantly mediated the effects of group on telomerase ($n = 38$; *point estimate* = 1.28; *BCa* = 0.29—3.4). *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

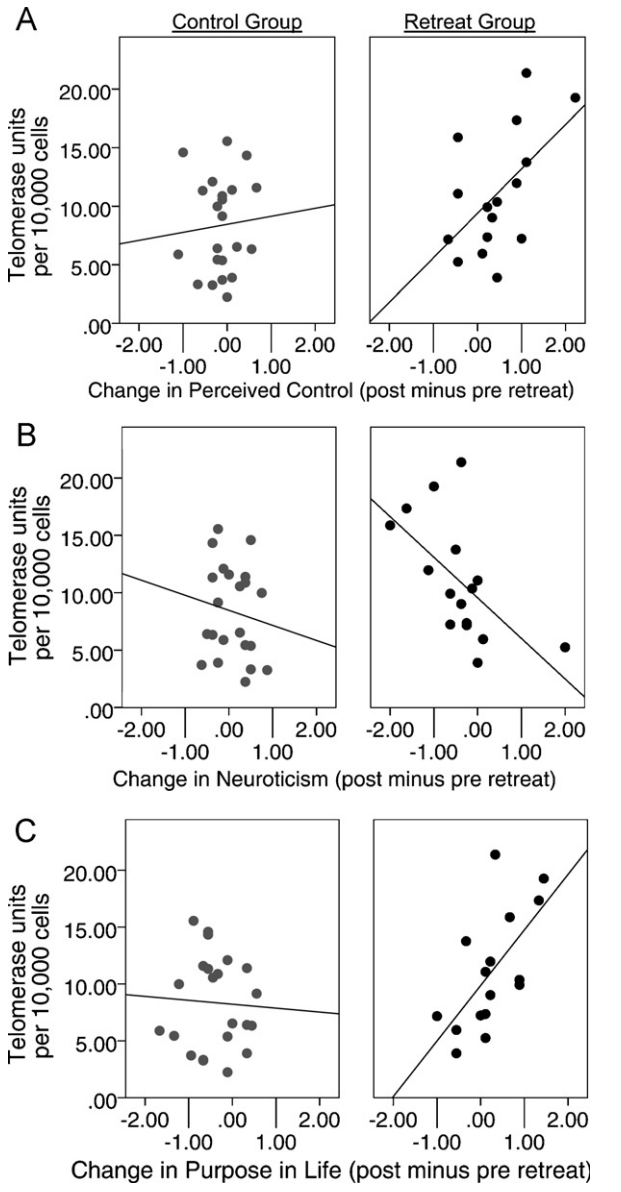

Figure 5 Post-retreat telomerase activity in controls (left) and retreat groups (right) as a function of changes in Perceived Control (top panel), Neuroticism (middle panel), and Purpose in Life (bottom panel) (see Fig. 4 for statistical approach and significance).

and negative coefficients for paths a and b (Fig. 5B) indicate that the more a participant's neuroticism decreased, the higher his or her level of post-retreat telomerase activity.

Changes in Purpose in Life also significantly mediated the group effect on telomerase (Figs. 4D and 5C; *point estimate* = 1.28; *BCa* = 0.29—3.4). That is, the group effect became non-significant after accounting for changes in Purpose in Life ($t = 0.83$, $p = 0.21$). A proportionate 0.48 of the total effect was explained by this indirect mediation. The positive point estimate indicates that the more a participant's sense of purpose increased, the higher his or her post-retreat telomerase activity.

Although BMI decreased in the retreat group, this change did not significantly affect post-retreat telomerase ($r = 0.10$, $p = 0.36$, one-tailed). Additionally, changes in BMI did not significantly explain the group difference in post-retreat telomerase (*point estimate* = 0.17, *BCa* = −0.07 to 1.86).

4.5. Changes in mindfulness or purpose in life mediate alterations in perceived control and neuroticism

Changes in Mindfulness significantly mediated retreat-related changes in Perceived Control (Fig. 6A). That is, the retreat vs. control group difference in changes in Perceived Control was significantly reduced (path c to path c′) after

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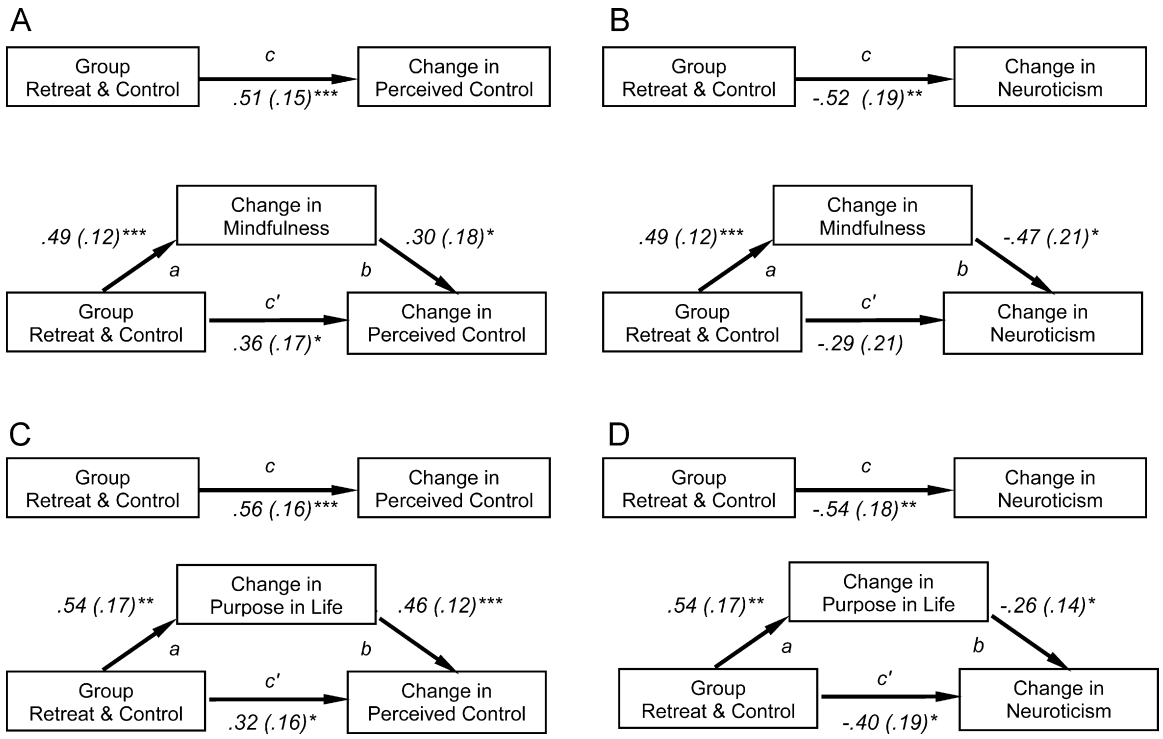

Fig. 6 Changes in Mindfulness and Purpose in Life were both significant partial mediators of the effect of Group on changes in Perceived Control and Neuroticism. Path values are unstandardized regression coefficients with standard errors in parentheses. Please see the text for *t*-test values that correspond to these regression coefficients. The following point estimates represent the mediated (indirect) effects derived from the (bootstrapped) product of paths a and b. (A) Changes in Mindfulness significantly mediated the effects of group on changes in Perceived Control ($n = 56$; *point estimate* = .15; *BCa* = 0.02—0.33). (B) Changes in Mindfulness significantly mediated the effects of group on changes in Neuroticism ($n = 56$; *point estimate* = —0.23; *BCa* = —0.45 to —0.09). (C) Changes in Purpose in Life significantly mediated the effects of group on changes in Perceived Control ($n = 58$; *point estimate* = 0.25; *BCa* = 0.11—0.48). (D) Changes in Purpose in Life significantly mediated the effects of group on changes in Neuroticism ($n = 58$; *point estimate* = —0.14; *BCa* = —0.31 to —0.04). *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

accounting for changes in Mindfulness (*point estimate* = 0.15, *BCa* = 0.02—0.33), with a mediated proportion of 0.29. The positive sign of the point estimate indicates that the more a participant's Mindfulness increased, the more his or her Perceived Control increased. However, a change in Mindfulness was only a partial (rather than a complete) mediator, with the direct effect (path c′) remaining significant ($t = 2.09$, $p = 0.02$), indicating that additional variables mediate this relation.

Similarly, changes in Mindfulness mediated retreat-related changes in Neuroticism (Fig. 6B). That is, the group effect on Neuroticism was significantly reduced (path c to path c′) after accounting for changes in Mindfulness (*point estimate* = —0.23, *BCa* = —0.45 to —0.09), with a mediated proportion of 0.44. The negative point estimate indicates that changes toward greater Mindfulness predicted reductions in Neuroticism. However, while the direct effect (path c′) was reduced to a non-significant relation, it did approach significance ($t = -1.42$, $p = 0.08$), suggesting that additional variables might also mediate this relation.

Changes in Purpose in Life significantly mediated retreat-related changes in Perceived Control (Fig. 6C), with the group effect significantly reduced after its inclusion (*point estimate* = 1.56, *BCa* = 0.24—3.9) and a mediated proportion of 0.43. Similarly, changes in Purpose in Life also significantly mediated meditation-related changes in Neuroticism (Fig. 6D), with the group effect significantly reduced after its inclusion (*point estimate* = —0.14, *BCa* = —0.31 to —0.04) and a mediated proportion of 0.30. The signs of both of these point estimates indicate that the more a participant's Purpose in Life increased, the more his or her Perceived Control increased and Neuroticism decreased. A change in Purpose in Life was also only a partial mediator for both these measures, with direct group effects on Perceived Control and Neuroticism remaining significant ($t = 1.98$, $p = 0.03$) and ($t = -2.10$, $p = 0.02$) after changes in Purpose in Life were taken into account.

4.6. Interpretation of mediated effects

Because the use of bootstrapping procedures for regression-based mediation is relatively new, a brief interpretation is provided here, using the data shown in Fig. 4B. The point estimate of 1.56 is the extent to which the group effect on telomerase is accounted for by a change in Perceived Control (path coefficients c—c′), which is mathematically equivalent to the product-of-coefficients (paths a*b). Therefore, telomerase values from participants in the retreat group are (on average) greater than the control group by 1.56 raw units of telomerase activity, which is explainable by the indirect path through changes in Perceived Control. This is only about half of the

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total observed group difference (see Fig. 2), explaining a proportionate 0.60 of the total effect (path coefficients a*b/c).

Because a given point estimate is derived from a large sampling distribution of point estimates (which is only normal when *n* is large), point estimates standardized to their error are not used to determine significance relative to a normal distribution. Rather, confidence intervals that have been corrected for skew and bias particular to each sampling distribution are used. The point estimate of 1.56 in Fig. 4B is therefore significant, as 0 is not contained within its corrected confidence interval.

4.7. Baseline effects

There is often a ''baseline effect'' in clinical intervention research whereby intervention effects are stronger for participants who were more at risk to begin with (at ''baseline''). In other words, initial functioning is often significantly related to changes in functioning. Increasingly, this effect is considered to be a finding rather than a variable to be controlled (Khoo, 2001; Tein et al., 2004; MacKinnon et al., 2007), because it is important to know who is most likely to benefit when designing future interventions.

A baseline effect occurred in the present study, where participants who reported less favorable psychological functioning at baseline improved the most from pre- to post-retreat: In the retreat group (after controlling for age and post-retreat BMI), psychological assessments at baseline were inversely related to changes (post minus pre-retreat) for Mindfulness ($r = -0.38$, $p < 0.05$), Purpose in Life ($r = -0.59$, $p < 0.0001$), Perceived Control ($r = -0.71$, $p < 0.0001$), and Neuroticism ($r = -0.45$, $p < 0.007$), after controlling for age. Because initial psychological function was significantly related to changes in psychological function, initial psychological function was also related to post-retreat telomerase activity: greater post-retreat telomerase activity was associated with lower baseline Perceived Control ($r = -0.66$, $p < 0.01$), lower baseline Purpose in Life ($r = -0.55$, $p < 0.05$), and approached a significant association with higher baseline Neuroticism ($r = 0.41$, $p < 0.08$).

The group effect on telomerase activity remained significantly mediated by changes in Purpose in Life, Perceived Control, and Neuroticism even after their baselines were treated as covariates [(*point estimate* = 1.07, *BCa* = 0.02—3.10), (*point estimate* = 1.37; *BCa* = 0.11—4.02), (*point estimate* = 1.53; *BCa* = 0.24—3.25)] (Due to limitations in sample size, the covariates of age and BMI were not included as covariates in models that included baseline psychological variables as covariates.) Even so, we regard the baseline effects as relevant findings (rather than problems to be controlled) and they suggest that the mediation effects reported here were stronger for participants who had higher baseline stress vulnerability, lower baseline stress resilience, and lower baseline Mindfulness and Purpose in Life.

5. Discussion

5.1. Summary

Telomerase is necessary to prevent early telomere shortening, which (on average) would foreshadow earlier than necessary mortality (Blackburn, 2000; Cawthon et al., 2003; Kim et al., 2003; Epel et al., 2009b). Interventions that may increase immune cell telomerase activity by altering perceived control and negative affectivity are clinically important, because with only two exceptions (Fauce et al., 2008; Ornish et al., 2008), there are no known pharmacological or behavioral interventions that have this beneficial effect. Telomerase is also inversely related to perceived stress (Epel et al., 2004), a psychological factor that can be reduced by meditative practice (e.g., Brown and Ryan, 2003; Nyklíčke and Kuijpers, 2008). Ours is the first study to examine relations between meditative practice and telomerase activity. We found that after intensive meditation training, retreat participants had significantly higher telomerase activity than the waitlist control group.

We also measured perceived control and negative affectivity (neuroticism), which became more favorable during the retreat and accounted for group differences in post-retreat telomerase activity. Further, this is the first study to consider 'meaning in life' as a quality developed by meditative practice that mediates retreat-related changes in stress resiliency and vulnerability, adding to previously reported findings that link ''benefit-finding'' (infusing a negative circumstance with meaning) with reduced psychological and physiological stress (Epel et al., 1998; Bower et al., 2008).

5.2. Integrating telomerase findings with those from previous studies

Greater telomerase activity in the retreat participants is consistent with a recent pilot study of participants with early-stage prostate cancer (Ornish et al., 2008), in which an increase in telomerase activity occurred in response to a comprehensive lifestyle change (which included a small amount of meditation or yoga). This increase was specifically related to a reduction in the number of self-reported ''intrusive thoughts'' related to their medical condition. Given that one aim of meditative practice is to reduce the negative impact of intrusive thoughts on well-being, it is plausible that the increase in telomerase activity reported in that study might have been due in part to meditation-induced changes.

Additionally, the association between changes in Perceived Control and Neuroticism and post-retreat telomerase activity in the present study are consistent with the previous report of an inverse relation between perceived stress and immune cell telomerase activity in caregivers of their chronically ill children (Epel et al., 2004). The present findings indicate that Perceived Control and negative emotionality, or Neuroticism, are two specific aspects of stress that might underlie this relation. We should note, however, one difference between these data and the findings of Epel et al. (2004): The present study focuses on how *changes* in psychological variables relate to post-retreat telomerase, rather than how these variables relate to telomerase at a single time-point. Using a cross-sectional approach, we did not find significant correlations between post-retreat psychological measures and post-retreat telomerase activity in the combined control and retreat groups (*r*-values ranged from −0.04 to −0.10). One reason for this result might be the potentially lower measurement error associated with the (within-subject) change scores as compared with the single post-retreat time point.

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It is difficult to determine the clinical relevance of the group difference in telomerase activity because of the paucity of studies measuring relations between telomerase activity and other factors, psychological or physiological. However, some understanding of this relevance might be found in Ornish et al. (2008), who found an increase of ~30% in telomerase activity following a comprehensive lifestyle change. Of clinical relevance, Ornish et al. measured a number of cardiovascular risk factors and found a significant correspondence between increased telomerase activity and decreased LDL cholesterol. Higher levels of telomerase activity have also been associated with lower levels of the stress hormone epinephrine (Epel et al., 2006). Although we are not able to directly compare the effect sizes of these previously reported effects with those of the present study, because of methodological differences, the evidence suggests that greater telomerase activity may be associated with reductions in specific cardiovascular risk factors. Finally, although several studies report relations between telomere length and both disease (Lin et al., 2009b) and psychological coping (Epel et al., 2009a), the clinical relevance of specific ranges of change in telomerase activity remains to be determined.

5.3. How might meditation result in beneficial changes: mindfulness?

Our meditation retreat was designed primarily to cultivate attentional skills and moment-to-moment awareness of a meditative object without distraction, which is an aspect of mindfulness that may generalize to the ability to maintain task-relevant attention (Indeed, in the same sample of meditation retreat participants, attentional skills improved significantly; see MacLean et al., 2010; Sahdra et al., in press). The model we tested here relied partly on the idea that enhanced task-relevant attention and focus (relative to attentional straying toward uncertainties and difficulties), may allow potentially stressful life circumstances and thoughts to be appraised as less threatening, thereby reducing psychological and physiological stress (Epel et al., 2009a). In other words, attentional training may enhance control of a person's thoughts and feelings, thereby allowing redirection of attention away from ruminative thinking and back to the present. Such changes in cognition should decrease negative affect (for a review of relevant literature, see Nolen-Hoeksema, 1998; Epel et al., 2009a). This idea is consistent with previous studies showing that dispositional mindfulness is associated with less alarming stress appraisals, more "approach" (active, problem-oriented) coping, and less avoidant coping (Heppner and Kernis, 2007; Weinstein et al., 2009). Our model is also consistent with findings that more adaptive coping mediates the relation between mindfulness and well-being (Weinstein et al., 2009) and longer telomere length (Epel et al., 2009a).

We tested the role of mindfulness as a mediator between meditation and telomerase activity and other psychological outcomes. Increases in mindfulness partially accounted for changes in two major contributors to stress: perceived control and neuroticism, although mindfulness did not significantly account for group differences in telomerase activity. This result suggests that mindfulness may exert effects on telomerase activity through variables involved in the stress appraisal process. Our limited sample size prevented the use of a more complex model to formally test this idea.

Because mindfulness is cultivated during meditation and is correlated positively with positive affect and negatively with neuroticism (e.g., Giluk, 2009), recent studies, as well as the present study, assign it a mediating role. Mindfulness may, however, have bidirectional relations with other mental processes: Although being more mindful might reduce the anxiety aroused by ruminative thoughts and increase the subjective sense of control associated with positive reappraisal (Garland et al., 2009, 2010; Borders et al., 2010), the converse may also occur. For example, feeling less anxious or more in control may result in greater mindfulness, an effect documented in studies in which induced states of anxiety adversely affected attention (Fox and Knight, 2005). To explore this issue in a preliminary way with the present data, we tested for reciprocal influences in two separate 'alternative directional models', with change in mindfulness as the dependent variable and change in perceived control or change in neuroticism as mediators. (As with the original directional model, 90% CIs were used for a one-tailed hypothesis and age was included as a covariate.) The mediated effect was significant both when perceived control was the mediator (*point estimate* = 0.08, *BCa* = 0.02—0.21; *proportion of mediated effect* = 0.19) and when neuroticism was the mediator (*point estimate* = 0.11, *BCa* = 0.02—0.25; *proportion of mediated effect* = 0.2). In comparison with the 'original directional models', however, the sizes of the mediated effects in the alternative directional models were reduced by ~30% for perceived control and ~50% for neuroticism.

These results suggest that mindfulness has a more robust causal effect on perceived control and neuroticism than they have on mindfulness. Although the training in the present study was specifically designed to improve aspects of mindfulness, and although the alternative directional models provide less support for mindfulness as a dependent variable than as a predictor, the question of how mindfulness relates to other variables remains to be answered. We draw only a tentative conclusion regarding the causal role of mindfulness and suggest that future studies include a more specific experimental manipulation of 'mindfulness' that is less entwined with other variables.

5.4. How might meditation result in beneficial changes: purpose in life?

Meditation and other contemplative practices also promote a sense of purpose and direction in life, as demonstrated here. This may occur as intentions and priorities shift away from hedonic pleasure to more genuine contentment and a greater sense of contributing to human welfare (Nanamoli and Bodhi, 1995; Wallace and Shapiro, 2006). Here, models that included a sense of purpose were based on the idea that broad appraisals of one's life as meaningful might affect situational stress appraisals, resulting in more flexible coping and greater stress resilience (Bower et al., 2008). This idea is consistent with previous research showing that greater meaning is associated with lower perceived psychological stress (e.g., Okamoto et al., 2007) and with some evidence showing that when a negative circumstance is infused with an

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over-riding and positive meaning, psychological coping improves and physiological stress responses are more adaptive (Folkman et al., 1997; Epel et al., 1998; Bower et al., 2008). Here, we found that retreat-related increases in Purpose in Life mediated changes in two major contributors to stress: perceived control and neuroticism. These increases in Purpose also mediated group differences in post-retreat telomerase activity. To our knowledge, these are the first data to consider meaning in life within the context of meditation training.

Because longitudinal studies suggest that the ability to find meaning in a stressful life event precedes changes in affect (for reviews, see Helgeson et al., 2006; Bower et al., 2008), and because Fredrickson et al. (2008) found it to be a mediating factor predicting life satisfaction and depressive symptoms, we considered it to be a causal factor in the present study. However, a sense of purpose in life may have bidirectional relations with perceived control and neuroticism. In an effort to explore this issue, we tested for reciprocal influences in two separate 'alternative directional models'. Change in purpose in life was analyzed as the dependent variable in two separate models, with the mediator being either change in perceived control or change in neuroticism (using a 90% CI for a one-tailed hypothesis and age as a covariate). Results indicated that the proportion of the mediated effect was significant in the alternative directional model with perceived control as a mediator (*point estimate* = 0.26, *BCa* = 0.12—0.48; *proportion of mediated effect* = 0.48) and in the model with Neuroticism as a mediator (*point estimate* = 0.13, *BCa* = 0.02—0.29; *proportion of mediated effect* = 0.24). These proportions are similar to those in the original directional models, suggesting that purpose in life may be reciprocally related to changes in perceived control and neuroticism.

Although the results of these alternative directional models appear to contradict Fredrickson et al.'s (2008) causal model, the direction of effects between our proposed mediators and our outcome variables is consistent with other previous research. Causality cannot be conclusively demonstrated here, however. For example, the causal model used by Fredrickson et al. (2008) suggests that meditative practice causes a gradual, daily accumulation of positive emotions that broaden the meditator's viewpoint, setting up a trajectory of growth in which the specific psychological resources of "purpose in life" and "mindfulness" expand, which in turn increases life satisfaction and reduces depressive symptoms. We did not test this particular model.

Interestingly, unlike other facets of well-being, Purpose in Life markedly declines with age (Ryff and Keyes, 1995). Meanwhile, among the elderly, those who report greater purpose have increased longevity and decreased mortality (Boyle et al., 2009). Because average telomere length predicts mortality (Cawthon et al., 2003; Epel et al., 2009b; Njajou et al., 2009), future research should consider the possibility that successful telomere maintenance may help to explain the relation between greater purpose in life and longevity. Although the sample we studied was small, it is provocative that purpose in life may reflect a cognitive shift that both reshapes two contributors to stress, neuroticism and low perceived control, and also promotes increased telomerase activity.

5.5. Limitations and future directions

The lack of a pre-test telomerase measure, the small sample size, limitations in the control group, and unusual sample characteristics require that our findings be regarded as tentative. These findings should be replicated in larger studies.

5.5.1. Baseline telomerase

Unfortunately, we did not have a baseline measure of telomerase, so our inference that telomerase activity increased as a result of meditation must be considered tentative. However, the inverse relations of baseline psychological function with changes in psychological function and with post-retreat telomerase activity in the retreat group suggest that this group may have had lower telomerase at pre-retreat (relative to post-retreat), possibly corresponding with their less favorable pre-retreat psychological function.

5.5.2. Control group limitations

Another limitation is that the control condition did not match the retreat condition in terms of being separated from the stresses and strains of daily life outside a retreat center. Although a placebo control condition in a retreat center, with alternative instruction being offered by the same meditation teacher, would have been ideal, it was not realistic. Our control group did have interests and backgrounds similar to those of the retreat group, and we did test both the retreat and control groups at the same time and in the same place, but the retreat group's removal from the stress of normal life for 3 months may have accounted, in part, for both the increase in telomerase activity and the improvements in psychological functioning in the retreat group.

We tried to address this limitation by performing several additional analyses. First, we determined whether the amount of time spent in meditation practice predicted changes in our study variables. Because the main focus of the retreat was Shamatha practice, we looked at the total amount of time spent in Shamatha meditation, as well as time spent in each specific type of this practice: (1) *mindfulness of breathing*, (2) *observing mental events, and* (3) *observing the nature of consciousness*. We found that the total amount of time spent practicing *mindfulness of breathing* predicted increases in self-reported Mindfulness, even after controlling for baseline (pre-retreat) Mindfulness and age ($r = 0.39$, $p = 0.02$, one tailed). The time spent in these meditation practices was not significantly related to changes in Purpose in Life, Perceived Control, Neuroticism, or telomerase, however ($p > 0.05$, one tailed, for all).

Second, we determined whether changes in psychological variables persisted ~5 months following the end of the retreat for all retreat participants, after they were back in their normal environments. We found that the beneficial changes that occurred from pre to post retreat significantly persisted at follow-up. In the retreat group, changes from pre-retreat to the follow-up were significant for Neuroticism ($t = 3.29$, $p = 0.04$), Perceived Control ($t = 1.82$, $p = 0.04$), and Mindfulness ($t = 2.27$, $p = 0.02$, one-tailed), but not for Purpose in Life ($t = 0.71$, $p = 0.36$). The persistence of these changes at follow-up was analyzed in relation to follow-up meditation practice, which was quantified as the number of hours (±SD) engaged in Shamatha practice since the end of

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the retreat ($M = 104.6 \pm 138.9$, *range* = 0–570). This relation was significant for Perceived Control ($r = 0.39$, $p = 0.03$, one tailed, after controlling for pre-retreat Perceived Control and age) and Mindfulness ($r = 0.34$, $p = 0.05$, one tailed, after controlling for pre-retreat Mindfulness and age). Together, the relation between Mindfulness and meditation practice and the persistence of the psychological changes at follow-up suggest that at least some of the changes cannot be explained simply by the participants being removed for 3 months from their customary daily lives.

We also acknowledge that retreat participants might have felt the need to respond favorably due to their substantial financial and motivational investments in being at the retreat. Because changes in psychological factors were correlated with post-retreat telomerase, we suggest that the motivation to merely *report* benefits is less of an issue than the motivation to actually *experience* benefits, as in well-documented cases of the placebo effect. However, it is difficult to assume that retreat participants in our study universally held positive expectations that were subsequently related to positive experiences: although affective experience may be related to prior expectation (Klaaren et al., 1994; Wilson et al., 1989), this may occur only for those who have certain personality characteristics (Besser and Shackelford, 2007). Moreover, higher Neuroticism has been linked to *negative* expectations for affective experiences, even for enjoyable activities such as pre-planned vacations (Besser and Shackelford, 2007). In the present data, those higher on Neuroticism at the outset tended to report greater affective benefit from the retreat (see 'baseline effects', in the results). This trend seems inconsistent with a cognitive dissonance interpretation of our results. Nevertheless, the issue of cognitive dissonance should be tackled more directly in future research by explicitly examining expectations of meditators at the outset and comparing them to objective outcomes of the training such as telomerase.

5.5.3. Statistical limitations due to small sample size

Several patterns were suggested by the data but not directly tested because of the limited sample size, but they should be considered in future studies. For example, our results suggest that mindfulness may affect telomerase activity through its influence on psychological stress, rather than directly. Additionally, both the correlations among the psychological variables and the proportions of indirect effects suggest that the mediation pathways through mindfulness and purpose in life might be relatively independent. Determining the relative independence of these indirect effects can be more properly tested using a multiple mediation model, where the two paths are tested and contrasted in parallel. Finally, the baseline effect (i.e., more improvement in participants who were worse off to begin with) might be modeled using pre-retreat psychological function as a moderator in separate mediation models (for different levels of baseline traits) to assess the relative sizes of indirect effects at various baseline values. This might provide more detailed information in tailoring interventions to specific populations. For example, Tein et al. (2004) incorporates baseline values using mediated baseline by treatment moderation. Although the use of change scores allowed us to model our results, which did not include a measure of baseline telomerase activity and were based on a small sample size, using change scores in regression and regression-based mediation analyses is controversial and we advise future investigators to use models that include baseline values as predictors when possible.

5.5.4. Differentiating types of meditation practice

Although the cultivation of attentional skills was the main focus of the meditation retreat in the present study, techniques intended to generate benevolent states (e.g., loving-kindness and compassion) were also taught and practiced. This is another specific avenue by which meditation might affect telomerase activity. For example, Pace et al. (2009) recently found that compassion meditation was associated with reductions in stress-induced behavioral and immune responses (i.e., interleukin and cortisol production), which are mediators that may affect telomerase (Lin et al., 2009b; Epel et al., 2009a). In our study it was not possible to distinguish between the effects of attentional training and the effects of techniques meant to generate benevolent thoughts and feelings.

5.5.5. Generalizing results

The participants in our study are not representative of the general population. The majority held advanced degrees, had a median income that was ~15K greater than the U.S. national average, and were able to leave their daily lives and travel to a remote retreat setting for 3 months. We do not know whether we would have observed the same effects in an urban retreat setting, where participants from a lower socioeconomic status practiced meditation during weekly classes. While prior research supports the possibility that the positive effects would occur even under these more usual conditions (e.g., Pace et al., 2009), more research is needed.

Another difference between our participants and the general population is that all of them had prior meditation experience, many had a long-term interest in meditation, and all were willing to leave their normal lives for 3 months to learn more about meditation. This unusual interest and motivation likely promoted perseverance while engaging in meditation practice. In turn, this may have contributed to the effects reported here, suggesting that these results may not generalize to the broader population, who might not possess the same degree of perseverance. This remains to be seen.

Although the present study requires replication and extension, it already points to previously unstudied psychological contributors to telomerase activity. By including specific hypotheses about psychological states and processes that are influenced by meditation and seem capable of affecting telomerase levels, we were able to propose several issues for future study that may lead to trainable practices that enhance both psychological well-being and physical longevity.

Role of funding sources

These data were collected as one part of The Shamatha Project, a large multimethod study investigating effects of intensive meditation training on cognition, emotion regulation, and physiological function. The Shamatha Project, in its entirety, was funded by Fetzer Institute Grant #2191 to Clifford

D. Saron, and by gifts from the Hershey Family, Chade-Meng Tan, Yoga Research and Education, Mental Insight Foundations, the Santa Barbara Institute for Consciousness Studies, the Baumann Foundation the Barney and Barbo Fund, and anonymous and individual donors, all to Clifford D. Saron. The Shamatha Project was additionally supported by a postdoctoral fellowship from the Social Sciences and Humanities Research Council of Canada to Baljinder K. Sahdra and a National Science Foundation predoctoral fellowship to Katherine A. MacLean. Sponsorship in the form of publicity for participant recruitment and discount services were provided by the Shambhala Mountain Center and in the form of an equipment loan by the Mind and Life Institute. With the exception of the Santa Barbara Institute, these funding sources and sponsors had no direct involvement in the present study design, data collection, data analysis, or the interpretation of findings and were not involved in writing up the present report or in the decision to present the paper for publication. Alan Wallace, President of the Santa Barbara Institute, contributed to subject selection and screening, instructed the retreat participants in meditation techniques for the entire 3 months, and clarified the conceptualization of traditional mindfulness within the written manuscript. He was not involved in data collection, analysis or interpretation of results of the study.

Conflict of interest

Dr.'s Epel, Lin, and Blackburn are co-founders of Telome Health, Inc., a company focused on measurement of telomere health. There are no other conflicts of interest.

Acknowledgements

We thank Dr. Allen Kanner for psychological prescreening of participants, Dr. Shiri Lavy for group stratification, Eileen Bartosch of the Red Feather Lakes Medical Center for collecting blood samples, the Shambhala Mountain Center for program support, C.D.S. lab staff and volunteers; Noelle Blalock and Center for Mind and Brain administrative staff; and our research participants and their families.

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Please cite this article in press as: Jacobs, T.L., et al., Intensive meditation training, immune cell telomerase activity, and psychological mediators. Psychoneuroendocrinology (2010), doi:10.1016/j.psyneuen.2010.09.010

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