Psychological Well-Being and Ill-Being: Do They Have Distinct or Mirrored Biological Correlates?

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Abstract

Background: Increasingly, researchers attend to both positive and negative aspects of mental health. Such distinctions call for clarification of whether psychological well-being and ill-being comprise opposite ends of a bipolar continuum, or are best construed as separate, independent dimensions of mental health. Biology can help resolve this query – bipolarity predicts 'mirrored' biological correlates (i.e. well-being and ill-being correlate similarly with biomarkers, but show opposite directional signs), whereas independence predicts 'distinct' biological correlates (i.e. well-being and ill-being have different biological signatures). *Methods:* Multiple aspects of psychological well-being (eudaimonic, hedonic) and ill-being (depression, anxiety, anger) were assessed in a sample of aging women (n = 135, mean age = 74) on whom diverse neuroendocrine (salivary cortisol, epinephrine, norepinephrine, DHEA-S) and cardiovascular factors (weight, waist-hip ratio, systolic and diastolic blood pressure, HDL cholesterol, total/HDL cholesterol, glycosylated hemoglobin) were also measured. *Results:* Measures of psychological well-being and ill-being were significantly linked with numerous biomarkers, with some associations being more strongly evident for respondents aged 75+. Outcomes for seven biomarkers supported the distinct hypothesis, while findings for only two biomarkers supported the mirrored hypothesis. *Conclusion*: This research adds to the growing literature on how psychological well-being and mental maladjustment are instantiated in biology. Population-based inquiries and challenge studies constitute important future directions.

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Introduction

Growing interest in positive psychology [1–4] raises a core question: is well-being merely the flip-side of studying psychological maladjustment, or do well-being and ill-being constitute separate, independent dimensions of mental functioning? The former view sees well-being and ill-being as opposite ends of a bipolar continuum, and thereby suggests that what has been learned about psychological distress and disorder is also definitive for well-being. Specifically, those with high levels of ill-being (e.g. depression) would be expected to show low levels of well-

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being (e.g. happiness, life purpose), and vice versa. The independence view, in contrast, asserts that well-being and ill-being are largely distinct domains of mental functioning, such that knowledge about the causes, consequences and correlates of one does not extrapolate to the other.

Research on positive and negative affect was the initial forum for asking questions about bipolarity versus independence, with early findings showing that the two types of affect were largely independent [5]. Although inversely correlated, the association between positive and negative affect was not strong (i.e. being high on one did not predict standing on the other). In addition, the two showed distinct correlates with other variables. This work spawned extensive subsequent inquiry that has continued to probe the bipolarity versus independence of positive and negative affect using quantitative, structural analyses [6–8].

Along the way, other studies documented that the absence of ill-being (e.g. depressive symptoms, or major depression) is no guarantee of possessing high well-being [9, 10]. In fact, some individuals show high levels of both ill-being and well-being, while others are free from major psychological disorders, but lack meaningful life engagement. At the level of neural circuitry, well-being and ill-being have also been shown to be differentially instantiated in the brain [11, 12]. In the clinical context, it has been observed that the long-term treatment of ill-being (i.e. recurrent depression) is not achieved solely by reducing negative cognition, but also requires promotion of well-being [13, 14].

Biology provides further opportunities for assessing whether well-being and ill-being are opposite sides of the same coin, or represent fundamentally distinct aspects of psychological functioning. The single continuum, bipolarity perspective predicts 'mirrored' outcomes (i.e. well-being and ill-being have largely similar biological correlates, but with opposite directional signs). In contrast, the independent perspective predicts 'distinct' biological correlates (i.e. well-being and ill-being have different biological signatures). Testing the mirrored versus distinct hypotheses is important for clarifying the extent to which positive psychology is *uniquely* consequential for understanding mind/body relationships, or is merely the flipside of extensive knowledge on biological underpinnings of mental distress and disorder. If the neurophysiological substrates of well-being [15] are different from those of ill-being, there may also be distinct mechanisms for preventing illness and disease including in contexts of known risk [16].

Psychological ill-being has been extensively linked with biology. For example, depressive symptoms and negative affect have been correlated with elevated cortisol and norepinephrine [17–20] as well as with increased cardiovascular risk [21, 22]. Trait anxiety has been associated with elevated glycosylated hemoglobin, elevated waist-hip ratio and depressed HDL cholesterol [22–24]. Trait anger, in turn, has been associated with greater morning to evening decline in salivary cortisol, elevated blood pressure and increased visceral adipose tissue [25–27].

Far fewer investigations have examined links between well-being and biology. High levels of purposeful life engagement (eudaimonic well-being) have been associated with significantly lower levels of cortisol as well as lower cardiovascular risk and musculoskeletal symptoms [28, 29]. Positive relations with others and purpose in life have also been linked with lower levels of inflammatory markers [30]. Similarly, social connectedness has been linked with lower resting blood pressure and lower levels of stress hormones (urinary epinephrine, norepinephrine, cortisol) [31]. And, self-enhancing thoughts have been linked with lower salivary cortisol and lower cardiovascular response to a laboratory stressor [32].

Rarely, if ever, have studies investigated psychological well-being, ill-being and biology *simultaneously*, thus allowing for direct tests of whether they have distinct or mirrored biological signatures. The present investigation addressed this question in a sample of aging women (aged 61–91) on whom detailed measures of well-being and ill-being were obtained. Multiple assessments of neuroendocrine factors (daily salivary cortisol, epinephrine, norepinephrine, DHEA-S) and cardiovascular risk (weight, waist-hip ratio, systolic and diastolic blood pressure, HDL and total/HDL cholesterol, glycosylated hemoglobin) were also obtained. Because prior research has documented age differences in well-being [33, 34], we also probed whether the biological correlates of well-being and ill-being differed between respondents in early versus later decades of aging.

Methods

Sample

The sample consisted of 135 women, all of whom had participated in a prior longitudinal study built around the transition of community relocation. Additional research support allowed for the recruitment of approximately half of the original sample for new data collection that included psychosocial assessments and a comprehensive array of biomarkers. There were no selection cri-

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teria, apart from being able to complete the questionnaires and visit the General Clinical Research Center (GCRC) for biological assessments. The newly recruited sample was not significantly different from the original sample with regard to health (chronic conditions, health symptoms), income, or marital status. However, the biomarker sample was significantly younger and had more education than the original sample. Biomarker respondents also had higher scores on four of six aspects of eudaimonic well-being compared with the original sample. The sample ranged in age from 61 to 91 (mean = 74.0; SD = 7.08). Respondents had moderate incomes (mean = USD 26,360; SD = USD 18,340) and slightly more than a high school education (mean = 14.1 years of schooling; SD = 2.8 years). Over half (55.6%) were widowed, with the rest married (17%), never married (8.9%), or divorced or separated (18.5%).

Well-Being Measures

Self-administered questionnaires were sent to respondents 3–4 weeks prior to their visit to the UW-Madison campus for the biomarker assessments. These were completed independently and returned to investigators at the time of their campus visit. Consistent with recent formulations [4], well-being was assessed with both eudaimonic and hedonic measures. The former addresses self-development and purposeful life engagement, while the latter focuses on happiness and contentment.

Eudaimonic Well-Being. Active engagement with the existential challenges of living was operationalized with six scales: autonomy, environmental mastery, personal growth, positive relations with others, purpose in life and self-acceptance. These were based on Ryff's [35] theoretical integration of numerous formulations of positive functioning. The hypothesized 6-factor structure of well-being has been supported by data from a national sample of Americans [36]. Recent work has also documented that eudaimonic well-being is empirically distinct from, yet related to hedonic well-being [3]. In this study, each well-being dimension was measured with 14 self-descriptive items (scale range = 14–84). Cronbach's alpha coefficients for the six scales ranged from 0.85 to 0.91. In the analysis, all eudaimonic scales were cubed to symmetrize the distribution of scores.

Hedonic Well-Being. Hedonic well-being was assessed with the positive affect scale of the PANAS Inventory [37]. The scale consists of 10 items that gather information about the respondent's affective state (scale range = 10–50). Items for positive affect included feeling interested, excited, strong, enthusiastic, proud, alert, inspired, determined, attentive and active. Respondents were asked to indicate the extent to which the descriptive terms comprising the scale characterize their feelings and emotions on an average day. Hedonic well-being was also assessed with the Positive affect scale of the short-form Mood and Anxiety Symptom Questionnaire (MASQ) [38]. This scale included 14 items (scale range = 14–70) that capture joy-in-living aspects of positive affect (e.g. felt happy, cheerful, optimistic, up, looked forward to things with enjoyment, having a lot of fun). Respondents answered how much they had felt this way during the past week. High scores indicate high positive affect. Alpha coefficients are 0.85 and 0.94, respectively, for the PANAS and MASQ positive scales. The two scales correlated 0.65 (p < 0.001) with each other. In the correlational analysis, the MASQ scale was squared to symmetrize the distribution of scores.

Ill-Being Measures

Psychological ill-being was measured in terms of four different assessments: negative affect, depressive symptoms, trait anxiety and trait anger. These are described below.

Negative Affect. Ten items (feeling distressed, upset, guilty, scared, hostile, irritable, ashamed, nervous, jittery, afraid) from the PANAS Inventory [37] were used to measure negative affect. Respondents indicated the extent to which these terms described their feelings on an average day. High scores indicate high negative affect. The alpha coefficient for these items was 0.89.

Depressive Symptoms. These were assessed using the CES-D Scale [39], a 20-item instrument (scale range = 0–60). Respondents answered each item with regard to how much they had experienced each symptom over the past week. High scores indicate high depressive symptoms. The alpha coefficient for depressive symptoms was 0.89.

Trait Anxiety. Ten items were used to operationalize trait anxiety [40]. The scale range was 10–40, with high scores indicating high trait anxiety. The alpha coefficient for this scale was 0.88. In the correlational analysis, the square root of this score was taken to symmetrize the distribution.

Trait Anger. Ten items were used to operationalize trait anger [40]. The scale range was 10–40, with high scores indicating high trait anger. The alpha coefficient for this scale was 0.92.

Biological Measures

Respondents were checked into the GCRC located within the UW Hospital and Clinics for an overnight stay. A trained nurse or physician took the respondent's medical history and conducted a physical health examination. GCRC nursing staff obtained blood samples and 12-hour urine samples. During these visits, respondents were given instructions and supplies for providing the daily saliva samples upon their return home.

Neuroendocrine Function. Biomarkers linked to neuroendocrine function included overnight urinary cortisol, daily salivary cortisol, overnight urinary epinephrine and norepinephrine, and from the fasting blood samples described above, DHEA-S. Urinary cortisol, epinephrine and norepinephrine levels were adjusted for urine creatinine levels. Urinary free cortisol levels were measured via radioimmunoassay at the ARUP Laboratory (Salt Lake City, Utah, USA). Urinary epinephrine and norepinephrine levels were measured via liquid chromatography at the University of Wisconsin Hospital and Clinics Clinical Laboratory. In the statistical analyses, the natural log of epinephrine was taken to symmetrize the distribution, and the square root of the norepinephrine values was taken for the same reason.

Subjects provided saliva samples three times a day for 4 days at home. The first sample was collected in the morning after the subject had been awake for 30 min, but before brushing teeth, drinking coffee or eating breakfast. The second sample was collected at midday, before eating lunch, and the third sample in the evening before brushing teeth and going to bed. Cortisol levels were measured with the Salimetrics (State College, Pa., USA) cortisol enzyme immunoassay kit. Prior to the assay, samples are centrifuged for 10 min at 5,000 rpm to remove cellular and bacterial debris that are inherent in saliva samples. Assay results were considered acceptable only if the coefficient of variation (CV) for the duplicate measurement of the sample was less than or equal to 20%. The mean inter-assay CV is 7.5%, and the mean intra-assay CV is 3.8%. The detection limit for this assay is 0.007 μg/dl.

Cardiovascular Function. Biomarkers linked to cardiovascular function included weight, waist-hip ratio, systolic and diastolic blood pressure, HDL and total cholesterol and glycosylated hemoglobin. Waist-hip ratio was calculated on the basis of waist circumference (measured at its narrowest point between the ribs and iliac crest) and hip circumference (measured at the maximal point of the buttocks). Systolic and diastolic blood pressure was calculated as the average of three blood pressure readings after 5 min of quiet sitting. Fasting blood samples for assays of HDL cholesterol, total cholesterol and glycosylated hemoglobin were obtained before 7:00 AM during the respondents' overnight stay at the GCRC. In the statistical analyses, the square root of weight was taken to symmetrize the distribution, and the natural log of glycoslyated hemoglobin was taken for the same reason.

Medications. Some respondents reported taking medications to treat high blood pressure or high cholesterol. All analyses pertaining to these biomarkers controlled for such medications. Analyses involving salivary cortisol also controlled for whether respondents reported taking any steroidal medications.

Statistical Analyses

Data analysis was conducted in multiple steps. First, frequency distributions for all measures (psychological and biological) were examined and symmetrized as needed. Such normalizing transformations were noted, where appropriate, in the above description of measures. Second, outliers were Winsorized [41], meaning that extreme observations (i.e. those above the 97th percentile and below the 3rd percentile) were replaced by the value of the nearest unaffected observation. Third, correlations for the full sample as well as for the age 75+ subsample were calculated between biomarkers and scales of well-being or ill-being. Using a per-comparison error rate, we identified correlations that were significantly different from zero at levels of 0.05, 0.01 and 0.001. They are reported in tables 1, 2.

Finally, significant coefficients from the above analyses were assembled in a table that clarified overall patterns of support for the distinct versus mirrored hypotheses. In this step, we also tested for significant differences between correlations of well-being or ill-being with the same biomarker. That is, for each significant effect obtained for a specific biomarker and well-being or ill-being, we investigated whether that correlation was significantly *different* from the parallel correlation for the *same* biomarker and ill-being or well-being, respectively. Confidence limits for these differences between correlated correlation coefficients, and the corresponding p values, were calculated using equations (1)–(4) in Meng et al. [42]. A multiple comparison adjustment was applied in these analyses. Comparisons that were significant controlling for false discovery rates of 0.05 are presented in table 3. For a detailed discussion of the false discovery rate and its rationale as a multiple comparison procedure see Benjamini and Hochberg [43].

Results

Well-Being, Ill-Being and Neuroendocrine Correlates

Table 1 presents bivariate correlations between scales of well-being or ill-being and neuroendocrine measures. Not included in the table are eudaimonic measures of environmental mastery and self-acceptance as well as both hedonic scales of positive affect as no significant effects were evident for these variables. Similarly, no significant effects were found for urinary cortisol, which is also not included in the table. With regard to salivary cortisol, significant positive associations were found between the average daily slope (3 assessments per day across 4 days) with personal growth and purpose in life, but only for the aged 75+ sample (n = 52). Directional patterns for these outcomes are clarified below. Epinephrine was positively correlated with positive relations with others, and norepinephrine was positively correlated with autonomy. With regard to ill-being, no significant effects were evident for negative affect or trait anxiety (scales not shown in the table). However, trait anger was positively correlated with epinephrine, and depressive symptoms (CES-D) were positively correlated with DHEA-S, but only for respondents aged 75+ (n = 66).

Figures 1 and 2 clarify the direction of effects for the average daily slope of salivary cortisol. The average slope ranged from strongly negative values (steeply downward slopes) to near zero (nearly flat slopes). Well-being scores (cubed to symmetrize distributions) plotted above these values show that those with higher personal growth and purpose in life had *flatter* daily slopes in salivary cortisol. Examination of the means at the three time points (early morning, mid-day, late evening) further revealed that those with higher personal growth and purpose in life *started the day with lower levels* of salivary cortisol and *stayed lower* throughout the day than those with lower levels of growth and purpose.

Well-Being, Ill-Being and Cardiovascular Correlates

Table 2 presents bivariate correlations between measures of well-being or ill-being with cardiovascular factors. No significant associations were evident for eudaimonic scales of autonomy, environmental mastery, or self-acceptance, or for the PANAS positive affect scale of hedonic well-being (scales not included in the table). Scores on positive relations with others were negatively linked with weight, waist-hip ratio and glycosylated hemoglobin. Positive relations with others remained a negative correlate of waist hip ratio even among those aged 75+, despite the reduction in sample size. Personal growth was positively correlated with HDL, the 'good' cholesterol, and negatively with the total-to-HDL cholesterol ratio. Purpose in life was also positively correlated with HDL cholesterol and negatively with waist-hip ratio. The MASQ positive affect scale was also positively correlated with HDL cholesterol.

Table 1. Correlations between measures of well-being, ill-being and neuroendocrine factors (n = 135, age = 61–91)

Neuroendocrine factors	Well-being[1]				Ill-being	
	positive relations	personal growth	purpose in life	autonomy	CES-D	anger (trait)
Salivary cortisol (daily slope)						
Age 75+ (n = 52)	0.10	0.29*	0.29*	–0.04	–0.16	–0.20
Epinephrine[2]	0.20*	0.02	0.02	0.002	0.002	0.24**
Norepinephrine[3]	0.08	0.06	–0.02	0.21**	–0.06	0.05
DHEA-S						
Age 75+ (n = 66)	–0.13	–0.08	–0.05	–0.08	0.26*	0.10

* $p < 0.05$, ** $p < 0.01$. Effect size (ES) ranges: * $0.40 < ES < 0.60$; ** $0.46 < ES < 0.51$.
[1] Well-being scales are cubed to symmetrize distributions.
[2] Natural log taken to symmetrize distribution.
[3] Square root taken to symmetrize distribution.

Table 2. Correlations between measures of well-being, ill-being and cardiovascular factors (n = 135, age = 61–91)

Cardiovascular factors	Well-being[1]				Ill-being			
	positive relations	personal growth	purpose in life	positive affect[2]	negative affect	CES-D	anxiety (trait)[3]	anger (trait)
Weight[3]	–0.26**	–0.07	–0.15	0.01	0.03	0.22**	–0.05	0.03
Waist-hip ratio	–0.32**	–0.15	–0.17*	–0.06	0.13	0.07	0.10	0.04
Age 75+ (n = 66)	–0.29*	–0.08	–0.16	–0.20	0.13	0.08	0.17	0.18
Systolic blood pressure	–0.09	–0.01	–0.09	0.12	–0.17*	–0.06	–0.15	–0.17*
Age 75+ (n = 66)	–0.08	0.11	–0.09	0.13	–0.35**	–0.15	–0.32**	–0.22
HDL cholesterol	0.16	0.18*	0.22**	0.18*	0.09	–0.13	–0.004	0.03
Total/HDL cholesterol	–0.10	–0.16*	–0.15	–0.13	0.08	0.11	–0.03	0.03
Glycosylated HG[4]	–0.21**	–0.10	–0.13	–0.10	0.20*	0.16	0.18*	0.25**
Age 75+ (n = 66)	–0.14	–0.20	–0.15	–0.11	0.23	0.17	0.16	0.41***

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Effect size (ES) ranges associated with corresponding p values: * $0.37 < |ES| < 0.6$; ** $0.42 < |ES| < 0.56$; *** $0.60 < |ES| < 0.70$.
[1] Well-being scales are cubed to symmetrize distributions.
[2] MASQ, squared to symmetrize distribution.
[3] Square root taken to symmetrize distributions.
[4] Natural log taken to symmetrize distribution.

With regard to ill-being, negative affect (PANAS) was negatively correlated with systolic blood pressure. This effect became notably stronger when the sample was limited to those aged 75+. Depressive symptoms (CES-D) were positively correlated with weight. Trait anxiety was negatively correlated with systolic blood pressure, but only for those aged 75+. Trait anxiety was also positively correlated with glycosylated hemoglobin. Finally, trait anger was also negatively correlated with systolic blood pressure and positively correlated with glycosylated hemoglobin. The latter finding was strongly evident for the full sample, but was particularly strong for the age 75+ sample (0.41***).

Overall Support for Distinct versus Mirrored Hypotheses

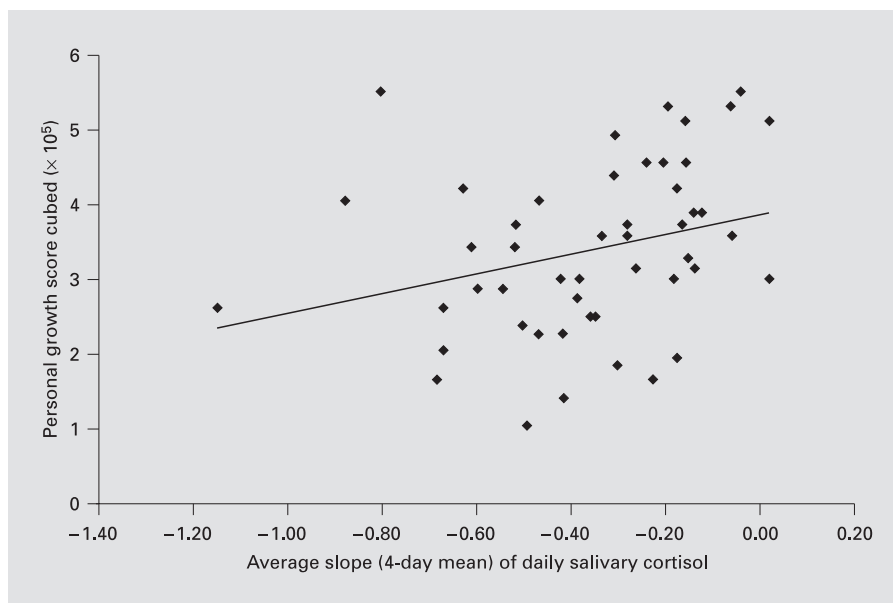Table 3 summarizes the above findings according to those showing support for the distinct versus mirrored

Fig. 1. Relationship between average slope of daily salivary cortisol and personal growth (older women aged 75+, n = 52).

Fig. 2. Relationship between average slope of daily salivary cortisol and purpose in life (older women aged 75+, n = 52).

hypotheses. The columns of the table divide the correlations of well-being and biomarkers into those with significant positive association, no significant link, or significant negative associations. The rows of the table divide the correlations of ill-being and biomarkers in the same fashion. The four dark-shaded cells identify outcomes that support the 'distinct' hypothesis – i.e., instances in which a significant association for well-being (or, respectively ill-being) with a specific biomarker was accompanied by a nonsignificant finding for measures of ill-being (or, respectively well-being) and the *same* biomarker. The two light-shaded cells (upper right, lower left) identify outcomes that support the 'mirrored' hypothesis, i.e. instances in which well-being and ill-being measures were both significantly correlated with the same biomarker, but with *opposite directional signs*. The two remaining unshaded cells (upper left, lower right) identify outcomes in which well- and ill-being scales correlated in the same direction with the same biomarker.

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Table 3. Ill-being, well-being and biomarkers: distinct or mirrored associational patterns

		Correlation of **well-being** with biomarkers		
		Positive associations	No associations	Negative associations
Correlation of ***ill-being*** with biomarkers	Positive associations	*Anger* ⇐ **Epinephrine** ⇒ Positive relations	*Depressive symptoms** ⇐ **DHEA-S**	*Negative affect* ← **Glycosylated** ➡ Positive *Anxiety* **hemoglobin** relations *Anger* *Depressive* ← **Weight** ➡ Positive *symptoms* relations
	No associations	**Cortisol** ⇒ Purpose in life Personal growth **Norepinephrine** ⇒ Autonomy **HDL cholesterol** ⇒ Purpose in life Personal growth Positive affect		**Waste-hip ratio** ➡ Positive relations ⇒ Purpose in life **Total HDL cholesterol** ⇒ Personal growth
	Negative associations		*Negative affect* ⇐ **Systolic** *Anxiety** **blood** *Anger* **pressure**	

☐ Distinct associational patterns; ☐ mirrored associational patterns.
⇨ Correlation is significantly different from zero (arrow pointing left = associations with *ill-being*; arrows pointing right = associations with well-being).
➡ Significant differences between correlation coefficients, adjusted for multiple comparisons by controlling the false discovery rate at 0.05.
* Age 75+ only.

Within each cell, the biomarker for which an effect was obtained is shown in bold. Arrows to the left of the biomarker identify significant associations with ill-being, while arrows to the right identify significant associations with well-being. Open arrows indicate correlations that were significantly different from zero, whereas filled arrows indicate instances in which there was a significant difference *between* the coefficients for well-being, or ill-being with the same biomarker (adjusting for multiple comparisons using a false discovery rate of 0.05).

Seven biomarkers (cortisol, norepinephrine, DHEA-S, waist-hip ratio, systolic blood pressure, HDL cholesterol, total/HDL cholesterol) revealed support for the distinct hypothesis. Three of these showed positive associations with well-being, but not ill-being. Specifically, those with higher levels of life purpose and personal growth had significantly flatter slopes of daily salivary cortisol, while those with higher levels of autonomy had higher levels of norepinephrine. Those with higher levels of purpose in life, personal growth and positive affect also had significantly higher levels of HDL cholesterol. Two other biomarkers showed significant negative associations with well-being, but not ill-being. Specifically, those with higher levels of positive relations and life purpose had lower waist-hip ratios, while those with higher levels of person-al growth had lower total/HDL cholesterol. The remaining two biomarkers showed significant associations with ill-being, but not well-being – those with more depressive symptoms showed higher levels of DHEA-S (full sample and age 75+), while those with higher levels of negative affect, trait anxiety (only 75+) and trait anger had lower levels of systolic blood pressure. With regard to significant differences between correlates of well-being or ill-being with the same biomarker, only the association of positive relations with waist-hip ratio was significantly different from the coefficients of three measures of ill-being (anger, anxiety, negative affect) with the same biomarker.

Two biomarkers (weight, glycosylated hemoglobin) revealed support for the mirrored hypothesis. Those with higher levels of negative affect, trait anxiety and trait anger (full sample and especially those 75+) had significantly higher levels of glycosylated hemoglobin, while those with higher levels of positive relations with others had significantly lower levels of this same biomarker. All of these ill-being and well-being outcomes were also significantly different from each other, as indicated by the bold arrows. Those with higher levels of positive relations with others also had lower weight, while those with greater depressive symptoms had higher weight. These two outcomes were also significantly different from each other.

The remaining effect in table 3 pertains to epinephrine, which was significantly and positively associated with both trait anger and positive relations with others. This finding conformed to neither the distinct nor mirrored hypothesis.

Discussion

The purpose of this investigation was to examine the empirical associations between measures of psychological well-being and ill-being with biomarkers, both neuroendocrine and cardiovascular. The findings are limited by the small sample of aging women on which the analyses are based and the cross-sectional design, which offers no insight on causal directionality (does well-being or ill-being influence biology, or does biology influence well-being or ill-being? or are they reciprocally related?). The study is also based on relatively simplistic bivariate analyses. Nonetheless, because few, if any, prior investigations have examined links between measures of positive and negative psychological functioning with biology *in the same study*, the findings offer a useful place to begin probing basic associations across wide territories of well-being, ill-being and biology.

The central question guiding the analyses was whether psychological well-being and ill-being constitute opposite ends of a bipolar continuum, which would predict similar biological correlates with opposite directional patterns (i.e. the mirrored hypothesis), or whether well-being and ill-being are largely independent dimensions of psychological functioning with unique biological correlates (i.e. the distinct hypothesis). The overall pattern of effects was more strongly supportive of the distinct hypothesis. For seven biomarkers, three neuroendocrine (cortisol, DHEA-S, norepinephrine) and four cardiovascular (HDL cholesterol, total/HDL cholesterol, systolic blood pressure, waist-hip ratio), significant correlations with well-being (or, ill-being) were not accompanied by significant associations with ill-being (or, well-being, respectively) and the *same* biomarker. Moreover, of the correlations that reflected the distinct pattern, the majority (69%) were instances in which measures of well-being were significantly correlated with biomarkers, but no parallel effects were evident for measures of ill-being. Stated another way, psychological well-being showed a more pervasive and distinct biological signature than was evident for psychological ill-being. However, it is important to note that these effects were evident for only a subset of the indicators of eudaimonic well-being (positive relations with others, purpose in life, personal growth). Surprisingly few significant associations were found for hedonic well-being.

Alternatively, for two biomarkers, namely weight and glycosylated hemoglobin, there was strong evidence of mirrored biological patterns. For both, it was the same measure of well-being (i.e. positive relationships with others) that showed significant differences with the opposite directional pattern obtained for measures of ill-being. Specifically, those with better social relationships had lower weight, while those with higher depressive symptoms had higher weight. Similarly, those with better social relationships had lower levels of glycosylated hemoglobin, while those with higher levels of negative affect, trait anxiety and trait anger had higher levels of the same biomarker. In addition, epinephrine was the single biomarker showing positive associational patterns both with well-being (positive relations with others) and ill-being (trait anger).

Although nearly all of the above findings conformed to the anticipated pattern that higher well-being would be associated with lower biological risk, and conversely, that higher ill-being would be associated with higher biological risk, there were select anomalies, the most notable of which was that higher levels of negative affect, anxiety and anger were significantly correlated with lower levels of systolic blood pressure. Whether this is a replicable finding remains to be seen, but we note that a community survey of persons aged 77–99 found that systolic hypotensive individuals had higher levels of negative affect than systolic normotensives [44].

In addition, because the obtained patterns are influenced by sample size and statistical power, important caveats surround any claims that the evidence supports a comparative advantage for the distinct hypothesis. With a larger sample size, some outcomes could well shift from support for the distinct to the mirrored pattern. For example, the positive relationships between slope of daily salivary cortisol and well-being (purpose in life, personal growth) was paralleled by an opposite, but nonsignificant effect of the same biomarker with trait anger. With a sample of 130+, this effect would have been significant, thereby supporting the mirrored pattern. Alternatively, with a larger sample size, there could also be increased evidence for distinct patterns, such as the overall number of significant effects between markers of HDL cholesterol or total/HDL cholesterol with well-being compared to links between these biomarkers and ill-being, where many notably weak associations were evident.

However provisional, these findings are nonetheless valuable in adding to the growing literature on how mental maladjustment and well-being are instantiated in biology. Such research increasingly clarifies that what has been learned from prior studies linking depressive symptoms, negative affect, anxiety and anger to various biomarkers, neuroendocrine and cardiovascular [17–27], does not automatically translate to efforts to map the biology of well-being [28–32]. Whether different mechanisms underlie psychological ill-being and well-being is far from clear, but the emerging work does call for greater attention to detailing both the type and level of biomarkers that constitute normal, healthy functioning as distinguished from those that indicate dysregulation.

Three types of inquiry will help move these agendas forward. The first requires population-level assessments to establish distributional characteristics (i.e. norms as to what constitutes low, average and high levels) of *both* psychological assessments (ill-being and well-being) and biomarkers. Such investigations are critically needed to clarify the generality of the psychobiological linkages across groups differentiated by gender, age, socioeconomic status and race/ethnicity. We note that even with our small sample of women, numerous correlates of well-being with biology (i.e. salivary cortisol) and ill-being with biology (e.g. DHEA-S, systolic blood pressure, glycosylated hemoglobin) were more strongly evident among those aged 75+, suggesting important life course dynamics in these relationships. Large, representative samples studied longitudinally are also well-suited for tracking downstream health consequences of such mind/body linkages. Which are predictive of subsequent profiles of morbidity and mortality, and which predict maintenance of healthy functioning through time? The juxtaposition of positive and negative mental conditions and how they are instantiated in biology will be central to answering these kinds of questions.

A second venue of future research builds on the distinction between psychological ill-being and well-being, but reminds us that in any given individual, they are combined into some blend of what James [45] referred to as 'healthy-mindedness', on the one hand, and the 'sick soul', on the other. Although the most straightforward combination sees them as inversely linked, there is ample evidence that the absence of mental maladjustment does not guarantee the presence of mental health [9, 10], nor does a prior history of mental illness obviate a future of psychological well-being [13, 14]. Unknown to date is what these differing combinations portend for biology and subsequent health.

Finally, the study of life challenges, both in the laboratory and naturalistically, provides an important direction for advancing knowledge of the dynamics of ill-being, well-being and biology. Particularly valuable is the opportunity to study recovery processes. For example, in a driving simulation challenge in the elderly [46] with cortisol assessments prior to the challenge and then every 15 min for 2.5 h, three categories of response were evident: (a) those showing a rapid initial rise in cortisol followed by a return to prechallenge levels within 45 min after completing the task; (b) those showing a rapid rise followed by persistently elevated cortisol postchallenge, and (c) those showing no response to the challenge. The first response, regarded as normal, may be predicted by those having high levels of well-being. Indeed, other analyses from these same respondents showed that those with high self-esteem showed this response profile [47]. Alternatively, high levels of ill-being may predict those who show persistently high levels of cortisol postchallenge. The nonresponse group, in turn, may reflect blunted sensitivity of the HPA axis (perhaps linked to prior mental health status), or the fact that high-speed driving simulation was not regarded as challenging.

Outside the laboratory, persistent challenges such as caregiving have also been linked with biological outcomes. A 6-year study of persons caring for a spouse with senile dementia showed increases in inflammatory markers, which were not evident for matched controls without caregiving responsibilities [48]. Caregivers had an average increase in levels of interleukin-6 (IL-6) that was 4 times greater than the increase seen for noncaregivers. These contrasting average profiles might be further illuminated by taking into account ratings of psychological well-being and ill-being, particularly given that the caregiving role has been previously linked with both heightened distress and enhanced well-being [49]. Those who find a deep sense of purpose, meaning and connection in the experience may not show the same cross-time increments in IL-6 that occur for those who find caregiving to be an adverse life stressor. Similarly, among noncaregivers, there may be those with high levels of ill-being who also show marked increments in IL-6 across time. Still, other studies have brought naturally occurring life challenges into the laboratory, for example, by observing online biological responses while couples discuss their marital conflicts [50]. Such studies have shown gender differences in physiological responses to marital conflict (i.e. older husbands exhibited greater cortisol response to conflict discussion, when spousal support was low, compared to wives). But again, this pattern could be sharpened by

taking into account the profiles of psychological ill-being or well-being that couples bring with them to these interactions. Those with pre-existing high levels of well-being, both male and female, may show less physiological reactivity to, or quicker recovery from, interaction about issues of conflict, compared with those with high profiles of ill-being.

Elaborating the features of adaptive responses to challenge – what some have referred to as the phenomenon of resilience [51] – will also advance these inquiries. Charney [51] has proposed that the 'resilient profile' is characterized by some of the same biomarkers studied here (i.e. high levels of DHEA-S, low levels of HPA axis activity, CRH and locus-coeruleus-norepinephrine activity) as well as high levels of neuropeptide Y, galamin, testosterone and 5-HT$_{1A}$ receptor and benzodiazepine receptor function. These constitute promising new directions for mapping the neurophysiological substrates of the resilient, who are also those likely to maintain high levels of psychological well-being in the face of life challenge [52].

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