A functional genomic perspective on human well-being

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To identify molecular mechanisms underlying the prospective health advantages associated with psychological well-being, we analyzed leukocyte basal gene expression profiles in 80 healthy adults who were assessed for hedonic and eudaimonic well-being, as well as potentially confounded negative psychological and behavioral factors. Hedonic and eudaimonic well-being showed similar affective correlates but highly divergent transcriptome profiles. Peripheral blood mononuclear cells from people with high levels of hedonic well-being showed up-regulated expression of a stress-related conserved transcriptional response to adversity (CTRA) involving increased expression of proinflammatory genes and decreased expression of genes involved in antibody synthesis and type I IFN response. In contrast, high levels of eudaimonic well-being were associated with CTRA down-regulation. Promoter-based bioinformatics implicated distinct patterns of transcription factor activity in structuring the observed differences in gene expression associated with eudaimonic well-being (reduced NF-κB and AP-1 signaling and increased IRF and STAT signaling). Transcript origin analysis identified monocytes, plasmacytoid dendritic cells, and B lymphocytes as primary cellular mediators of these dynamics. The finding that hedonic and eudaimonic well-being engage distinct gene regulatory programs despite their similar effects on total well-being and depressive symptoms implies that the human genome may be more sensitive to qualitative variations in well-being than are our conscious affective experiences.

social genomics | gene regulation

Psychological well-being has been shown to forecast future physical health above and beyond its association with current physical health (1–6), and above and beyond its association with reduced levels of stress, depression, and other negative affective states (2, 3, 5–11). However, the biological basis for this relationship remains poorly understood, in part because of a paucity of information regarding the molecular signaling pathways that transduce positive psychological states into somatic physiology (12), and in part because of the multidimensional nature of human well-being (6, 13).

Philosophers have long distinguished two basic forms of well-being: a "hedonic" form representing the sum of an individual's positive affective experiences, and a deeper "eudaimonic" form that results from striving toward meaning and a noble purpose beyond simple self-gratification (6, 13–16). Both dimensions of well-being are deeply implicated in human biology and evolution (17–24), with hedonic well-being hypothesized to motivate basic physiological and psychological adaptations, and eudaimonic well-being hypothesized to motivate more complex social and cultural capacities (17–19, 25, 26). Although hedonic and eudaimonic well-being are conceptually distinct, they are empirically correlated (14, 27) and can reciprocally influence each other (28, 29). As a result, it has been difficult to determine from observational epidemiology which form of human well-being is most directly related to physical health and longevity (6). It has also been difficult to determine whether hedonic and eudaimonic well-being engage similar biological processes, or whether they have distinct physiologic consequences (although refs. 13, 30, and 31 provide some initial explorations).

In the present study, we examined the biological implications of hedonic and eudaimonic well-being through the lens of the human genome—a system of ∼21,000 genes that has evolved fundamentally to help humans survive and thrive (i.e., be well) (32). Previous studies have found that circulating immune cells show a systematic shift in basal gene expression profiles during extended periods of stress, threat, or uncertainty (12, 33). This conserved transcriptional response to adversity (CTRA) is characterized by increased expression of genes involved in inflammation (e.g., proinflammatory cytokines such as *IL1B*, *IL6*, *IL8*, and *TNF*) and decreased expression of genes involved in type I IFN antiviral responses (e.g., *IFI*-, *OAS*-, and *MX*- family genes) and IgG1 antibody synthesis (e.g., *IGJ*) (12, 33–35). The CTRA transcriptional program likely evolved to help the immune system counter the changing patterns of microbial threat ancestrally associated with changing socioenvironmental conditions (e.g., increased risk of wound-related bacterial infection associated with experienced threat or social conflict vs. increased risk of socially mediated viral infection associated with affine social contact) (12, 33, 36). However, in the very different environment of contemporary human society, chronic CTRA activation by social or symbolic threats may promote inflammation-mediated cardiovascular, neurodegenerative, and neoplastic diseases and impair host resistance to viral infections (12, 33, 37). The present analysis used the CTRA gene expression profile as a high-dimensional molecular reference space in which to map the potentially distinct biological effects of hedonic and eudaimonic well-being.

Results

Differential expression of the leukocyte CTRA was assessed in genome-wide transcriptional profiles of peripheral blood mononuclear cells (PBMCs) sampled from 80 healthy adults recruited from the Chapel Hill, NC, area and assessed for hedonic and eudaimonic well-being. Table 1 reports sample characteristics and correlates of each dimension of well-being. Individuals differed widely in their levels of hedonic and eudaimonic well-being, with status varying across the majority of the assessment instrument's six-point frequency metric (Short Flourishing Scale) (38) (Fig. 1*A*). As previously observed (6, 14, 27), hedonic and eudaimonic well-being were positively correlated ($r = 0.79$; $P < 0.0001$).

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Table 1. Sample characteristics

Characteristic	Value	*r* (*P* value) for association* With Hedonic	With Eudaimonic
Age, y	48.1 ± 8.1	+0.02 (0.8545)	−0.01 (0.9447)
Female sex, %	60.0	+0.01 (0.9481)	+0.02 (0.8663)
Race/ethnicity, %	—	NA (0.1592)†	NA (0.3536)†
White	61.5	—	—
Black	30.1	—	—
Hispanic	3.6	—	—
Asian	4.8	—	—
Body mass index, kg/m^2	28.8 ± 7.1	−0.22 (0.0433)	−0.17 (0.2073)
Smoking history, %	15.7	−0.05 (0.6869)	+0.05 (0.6470)
Alcohol history, %	64.2	+0.18 (0.1045)	+0.07 (0.5540)
Depression (CES-D), 0–60 scale	12.8 ± 10.5	−0.65 (0.0001)	−0.64 (0.0001)
Minor illness symptoms, 0–8 scale‡	0.9 ± 0.9	−0.20 (0.0757)	−0.27 (0.0222)

Values presented as mean ± SD where appropriate. NA, not applicable.
**P* value for simple (unadjusted) association (*r* or *F*).
†*P* values derive from one-way ANOVA testing for differences in eudaimonic and hedonic well-being as a function of race/ethnic group.
‡Frequency of 13 minor illness symptoms during the previous 2 wk, each rated from 0 (not at all) to 8 (very frequently).

Average levels of hedonic well-being exceeded average levels of eudaimonic well-being across the sample as a whole (hedonic, mean = 3.75 ± 0.11 SEM; eudaimonic, 3.17 ± 0.12; difference, $P < 0.0001$). Only 22% of study participants showed levels of eudaimonic well-being that exceeded their level of hedonic well-being (i.e., eudaimonic predominance; sign test, $P < 0.0001$; Fig. 1*B*).

Negative Affective Correlates of Well-Being. Hedonic and eudaimonic well-being may potentially engage different levels of negative affect as a result of eudaimonic subordination of hedonic self-gratification (6, 14). However, analyses found both forms of well-being to show similarly strong inverse relationships to symptoms of depression [Center for Epidemiological Studies–Depression (CES-D) correlation with hedonic well-being, $r = -0.67$, $P < 0.0001$; correlation with eudaimonic well-being, $r = -0.66$, $P < 0.0001$; difference in dependent correlations, $P = 0.8550$]. Similarly strong inverse relationships were also observed for CES-D subscales assessing affective symptoms of depression (hedonic, $r = -0.75$, $P < 0.001$; eudaimonic, $r = -0.71$, $P < 0.001$; difference, $P = 0.3228$) and vegetative symptoms of depression (hedonic, $r = -0.45$, $P < 0.001$; eudaimonic, $r = -0.48$, $P < 0.001$; difference, $P = 0.6297$).

CTRA Transcriptome Profile. Primary analyses examined the relationships of hedonic and eudaimonic well-being to expression of a 53-gene contrast score summarizing three a priori-defined components of the CTRA profile (12, 33–35): up-regulated expression of proinflammatory genes, down-regulated expression of genes mediating type I IFN responses, and down-regulated expression of genes involved in antibody synthesis. General linear model analyses quantified the association between expression of each of the 53 CTRA contrast genes and levels of hedonic and eudaimonic well-being [each well-being dimension treated as a continuous measure and adjusted for correlation with the other dimension of well-being and for age, sex, race/ethnicity, body mass index (BMI), smoking, alcohol consumption, recent minor illness symptoms, and leukocyte subset prevalence; *SI Methods*]. Contrast coefficient-weighted association statistics were averaged to summarize the magnitude of association over the entire CTRA gene set. CTRA gene expression varied significantly as a function of eudaimonic and hedonic well-being (Fig. 2*A*). As expected based on the inverse association of eudaimonic well-being with depressive symptoms, eudaimonic well-being was associated with down-regulated CTRA gene expression (contrast, $P = 0.0045$). In contrast, CTRA gene expression was significantly up-regulated in association with increasing levels of hedonic well-being ($P = 0.0047$). Follow-up analysis of specific gene subsets linked higher levels of eudaimonic well-being to up-regulated expression of type I IFN response genes ($P = 0.0084$) and a trend toward up-regulated expression of antibody synthesis genes ($P = 0.0849$; Fig. 2*B*). In contrast, higher levels of hedonic well-being were associated with up-regulated expression of proinflammatory genes ($P = 0.0008$) and a trend toward down-regulated expression of antibody synthesis genes ($P = 0.0776$; Fig. 2*B*).

To ensure that differential gene expression estimates were not distorted by the high correlation of hedonic and eudaimonic well-being (39), we conducted ancillary analyses in which the 2D well-being space was reparameterized in terms of total well-being (i.e., hedonic plus eudaimonic) and relative eudaimonic predominance (i.e., eudaimonic minus hedonic). These reparameterized dimensions were only modestly correlated ($r = 0.21$; $P = 0.0610$; Fig. 1*B*). Simultaneous analysis of both reparameterized dimensions showed no differential expression of the CTRA profile as a function of total well-being (mean = −0.54 ± 2.93% difference in contrast gene expression over the range [−2 SD, +2 SD] relative to mean level of total well-being; $P = 0.8530$). However, eudaimonic predominance was associated with significant down-regulation of the CTRA gene expression profile (−4.52 ± 1.27% over [−2 SD, +2 SD]; $P = 0.0010$). The latter effect stemmed primarily from down-regulation of proinflammatory genes (−8.50 ± 3.45% over [−2 SD, +2 SD]; $P = 0.0016$).

Transcription Control Pathways. To assess the role of immunoregulatory transcription factors previously implicated in CTRA-related gene expression (proinflammatory NF-κB and activator protein 1 (AP-1) factors and type I IFN-related STAT and interferon response factor (IRF) factors) (12, 33–35), we applied Transcription Element Listening System (TELiS) promoter-based bioinformatics analyses (40) to all genes showing ≥1.5-fold difference in average expression over the range from −2 SD to +2 SD relative to the sample mean on each dimension of well-being (hedonic, 92 transcripts up-regulated and 52 down-regulated; eudaimonic, 65 up-regulated and 123 down-regulated; genes listed in Datasets S1 and S2). Analyses of genes regulated in association with eudaimonic well-being indicated up-regulated

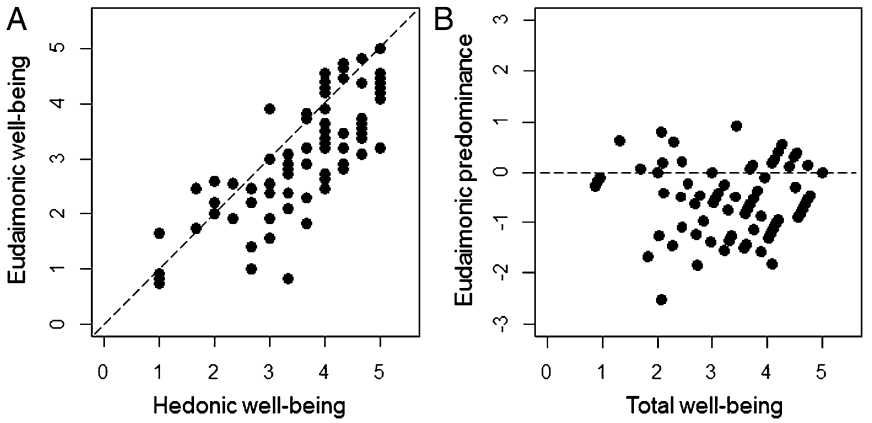

Fig. 1. (*A*) Relationship between hedonic and eudaimonic well-being (dashed line indicates equivalent levels; $n = 80$). (*B*) Tukey mean-difference plot (39) reexpressing individual differences in well-being in terms of total well-being (hedonic plus eudaimonic) and eudaimonic predominance (eudaimonic minus hedonic; dashed line indicates equivalent levels).

activity of IRF and STAT family transcription factors and marginally down-regulated activity of NF-κB and AP-1 factors (Fig. 3*A*). However, none of these basic immunoregulatory transcription factors was implicated in the transcriptional effects of hedonic well-being (Fig. 3*A*). Transcription factor results were shown to be reliable in split-half replication studies ($r = 0.71$) and Monte Carlo analyses of statistical power and result replicability (Figs. S1–S5).

Cellular Origins. To determine whether the transcriptional correlates of well-being might occur within the same leukocyte subpopulations previously shown to mediate the CTRA transcriptional effects of adverse experience (i.e., monocytes, dendritic cells, and B lymphocytes) (34–36, 41, 42), we conducted transcript origin analysis (TOA) (36) on differentially expressed genes (Datasets S1 and S2). Results identified monocytes and plasmacytoid dendritic cells (pDCs) as primary carriers of genes up-regulated in hedonic well-being and primary carriers of genes down-regulated in eudaimonic well-being (Fig. 3*B*). B lymphocytes predominately contributed genes down-regulated in hedonic well-being and genes up-regulated in eudaimonic well-being. Results of cellular origin analyses were found to be reliable in split-half replication studies ($r = 0.82$ for eudaimonic association and $r = 0.79$ for hedonic; Figs. S6 and S7) and in Monte Carlo analyses of statistical power and result replicability (Figs. S1–S5).

Discussion

The results of this study show that hedonic and eudaimonic well-being, although correlated, have markedly divergent gene transcriptional correlates in human immune cells. Eudaimonic well-being was associated with decreased expression of the previously defined CTRA transcriptome profile involving elevated expression of proinflammatory genes and reduced expression of genes involved in antibody synthesis and type I IFN antiviral responses (12, 33–35). In contrast, hedonic well-being was associated with significant up-regulation of the CTRA gene expression profile. These opposing transcriptome profiles emerged despite the fact that hedonic and eudaimonic well-being were experienced similarly at the level of conscious affect (i.e., they showed comparably strong positive relationships to total well-being and comparably strong inverse relationships to depressive symptoms, and were highly correlated with one another). The observed differences in gene expression were also independent of demographic, health, and behavioral risk factors (age, sex, race/ethnicity, BMI, smoking, alcohol consumption, minor illness symptoms), independent of variation in the distribution of leukocyte subsets within the circulating PBMC pool, and robust to reparameterization of the 2D well-being space to mitigate the collinearity of hedonic and eudaimonic well-being. In reparameterized analyses, CTRA gene expression did not vary as a function of total well-being (hedonic plus eudaimonic), but it was significantly down-regulated among individuals showing a relative predominance of eudaimonic vs. hedonic well-being. The emergence of distinct leukocyte transcriptome profiles in the presence of similar affective profiles suggests that the gene regulatory architecture of the human immune system may be more sensitive to the eudaimonic vs. hedonic sources of human happiness than are our conscious experiences.

Bioinformatic analyses of the gene expression differences associated with hedonic vs. eudaimonic well-being implicated several of the same cellular mediators and transcription control pathways previously linked to CTRA activation in adverse life circumstances such as low socioeconomic status, social isolation, diagnosis with a life-threatening disease, and imminent bereavement

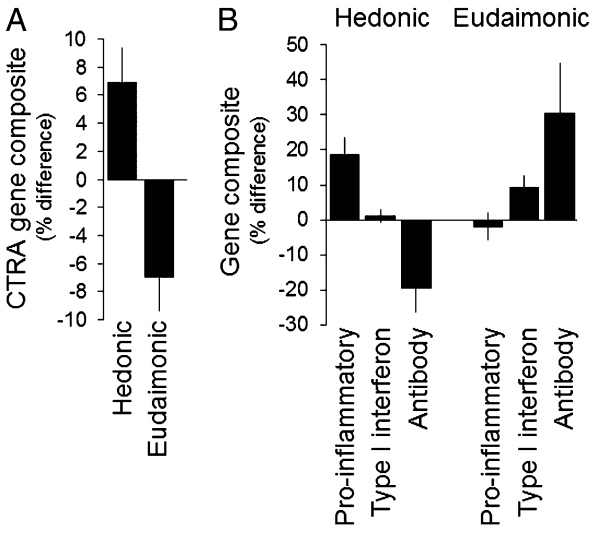

Fig. 2. Expression of the CTRA gene set. (*A*) Linear model-based estimates of mean difference (±SEM) in expression in a 53-gene CTRA contrast score in PBMCs from individuals with low levels (−2 SD relative to sample mean) vs. high levels (+2 SD) of hedonic well-being and eudaimonic well-being (each adjusting for the other and for demographic and behavioral covariates). (*B*) Differential expression of CTRA subcomponents: 19 proinflammatory genes, 31 type I IFN response genes, and three antibody synthesis genes.

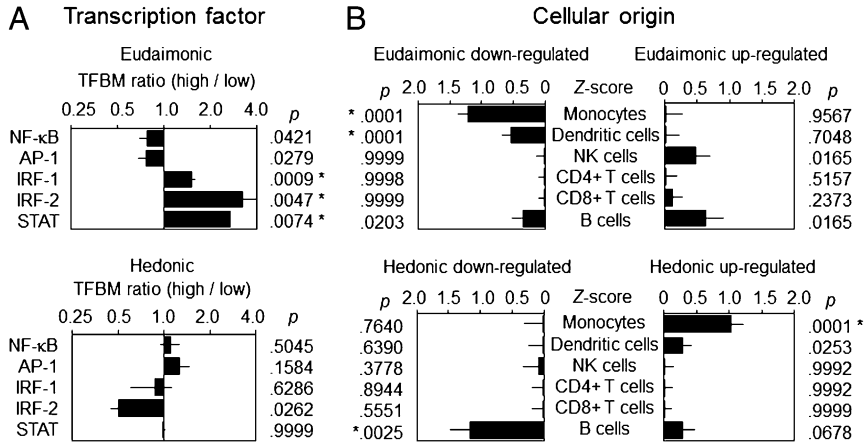

Fig. 3. Transcription control pathways and cellular origin. Genes showing ≥1.5-fold differential expression across low levels (−2 SD relative to sample mean) vs. high levels (+2 SD relative to sample mean) of eudaimonic well-being and hedonic well-being were tested for (*A*) differential activity of specific transcription factors as indicated by TELiS analysis of transcription factor-binding motifs (TFBM) in proximal promoter sequences of up- vs. down-regulated genes (40) and (*B*) PBMC cell type of origin as indicated by TOA cell-type diagnosticity *z*-scores (36). (*$P < 0.05$ after control for multiple hypothesis testing.)

(12, 33–35). In promoter-based bioinformatics analyses of transcription factor activity, eudaimonic well-being showed a regulatory profile inverse to that previously associated with adverse life circumstances (i.e., reversal of CTRA-related up-regulation of proinflammatory NF-κB and AP-1 transcription factors and down-regulation of antiviral IRF and STAT factors) (12, 33–35). However, none of these basic immunoregulatory transcription factors was implicated in the transcriptomic effects of hedonic well-being. Transcript origin analyses also identified monocytes, pDCs, and B lymphocytes as cellular mediators of well-being's effects on gene expression, but in a reciprocal pattern for its hedonic and eudaimonic dimensions (i.e., monocytes and pDCs were implicated in eudaimonic gene down-regulation, and monocytes and B lymphocytes were implicated in eudaimonic gene up-regulation). In conjunction with the analyses of transcription factor activity, these results suggest that the divergent gene expression profiles observed in hedonic and eudaimonic well-being are mediated by activation of distinct receptor systems within a fixed set of environmentally responsive cell types (33). These findings mirror results from previous studies of adverse experience in identifying a similar set of target cells (34, 36, 41, 42), with eudaimonic well-being in particular showing a reversal of CTRA-related transcription factor dynamics (12, 33). These results identify specific psychological, cellular, and molecular targets for future analyses of the social signal transduction pathways that mediate the prospective health advantages of psychological well-being (1–11).

In interpreting these results, it is important to note that hedonic and eudaimonic well-being are not mutually exclusive approaches to happiness, nor do they represent a simple typology or a tradeoff. Both types of well-being share some common sources (e.g., perceived social connections) (29) and can reciprocally influence one another (29) [i.e., positive affect predisposes people to find positive meaning (43, 44), and finding positive meaning increases positive affect (45)]. As such, the current finding that a purified index of eudaimonic well-being (purged of shared variance with hedonia) predicts a more favorable pattern of gene expression than does a purified index of hedonic well-being (purged of shared variance with eudaimonia) says more about which form of well-being one would not want to do without, rather than which form one would be better to avoid. For people in whom one form of well-being outweighs the other, striving predominately toward meaning may have more favorable effects on health than striving predominately toward positive affect per se. An important topic for future research will be to define which specific sources of well-being are most generative of eudaimonia and health (e.g., social pleasures such as connecting with others, cognitive pleasures such as taking in new ideas, spiritual pleasures such as connecting to something larger than the self, and creative pleasures such as generating new knowledge or works of art) (13, 15).

The present findings are limited in several respects. These results come from a cross-sectional analysis, and the observed associations may reflect a causal effect of immune biology on affect or social behavior (46, 47). However, that is unlikely to explain the associations observed here because experimentally induced inflammation generally reduces hedonic well-being (6, 46, 47) whereas these findings link inflammatory gene expression to elevated hedonic well-being. Nevertheless, direct experimental manipulations of hedonic and eudaimonic well-being will be required to clearly define their causal effects. No direct measure of immune system functional activity is available here (e.g., effector response to an immunologic challenge), so the health significance of these gene expression dynamics remains to be determined. However, the observed up-regulation of antibody synthesis genes in eudaimonic well-being is consistent with previous data showing enhanced antibody response to vaccination in people with high levels of well-being (48, 49). The observed down-regulation of proinflammatory genes in eudaimonic well-being is also consistent with previous studies of protein biomarkers of inflammation and other cardiovascular risk factors (6, 13, 30, 31, 50, 51). This study focuses on a one-time analysis of immune cell gene expression in a predominately white US sample, and replication of these findings in other populations with longitudinal assessment of well-being and biology will be required to gauge generality and consistency of these effects. In the context of the present sample, split-half replication studies and Monte Carlo power analyses indicated that the observed associations involving specific a priori-defined gene sets are reliable (Figs. S1–S3, S6, and S7). This study was not designed for de novo discovery of reliable associations between specific individual transcripts and well-being phenotypes. The low-level point estimates of association in Datasets S1 and S2 serve only as inputs into high-level bioinformatics analyses of CTRA-related cell types and transcription factors, and should not be considered statistically reliable at the individual gene level. The high-level bioinformatic results emerging from these analyses are consistent with previous direct assays of target cell type and transcription factor activity (12, 33), but the present results require direct verification in future studies. The gene expression dynamics observed here can only be interpreted in the context of immune

cells, and the effects of well-being on transcriptomes in the central nervous system and other tissues remains an important topic for future research. The measure of well-being used here provides valid and reliable assessments of general hedonic and eudaimonic well-being (38, 52) (e.g., in this sample, Cronbach α values are 0.93 and 0.92 for those two respective domains), but defining the specific aspects of eudaimonia that relate most directly to gene expression [e.g., as has been done for other health-related biomarkers (13, 30, 31)] will require more extensive measurement of the constituent dimensions of eudaimonia in future studies (13, 15, 30, 53).

Hedonic and eudaimonic well-being were originally distinguished to resolve basic and ancient philosophical questions regarding the best way for humans to live (14, 16, 53, 54). The present data offer little grounds to prefer one mode of happiness over the other based on affective experience, but they identify a stark contrast at the level of molecular physiology. If "the good life" is a long and healthy life free from the allostatic load of chronic stress, threat, and uncertainty (55, 56), CTRA gene expression may provide a negative reference point for how not to live [figuratively in its association with adverse experience (12, 33) and literally in its expression of disease-promoting genes (37)]. If we ask which type of happiness most directly opposes that molecular antipode, a functional genomic perspective favors eudaimonia. Genomics-based analyses also reveal an adverse molecular physiology of hedonic well-being that appears not to register at the level of experienced affect. This dissociation of molecular well-being from affective well-being implies the potential for an objective approach to moral philosophy rooted in the utility of health and the basic biology of human nature (57–59) as revealed in 2 million years of evolved genomic programming to help human beings survive and thrive in this world (32).

Methods

Participants and Study Procedure. A total of 84 healthy adults were recruited from the Durham and Orange County regions of North Carolina by community-posted flyers and e-mail advertisements followed by telephone screening to assess eligibility criteria, including age 35 to 64 y, written and spoken English, and absence of chronic illness or disability. Following written informed consent, participants completed online assessments of hedonic and eudaimonic well-being [Short Flourishing Scale, e.g., in the past week, how often did you feel. . . happy? (hedonic), satisfied? (hedonic), that your life has a sense of direction or meaning to it? (eudaimonic), that you have experiences that challenge you to grow and become a better person? (eudaimonic), that you had something to contribute to society? (eudaimonic); answered on a six-point frequency metric whereby 0 indicates never, 1 indicates once or twice, 2 indicates approximately once per week, 3 indicates two or three times per week, 4 indicates almost every day, and 5 indicates every day] (38, 52) and depressive symptoms (per CES-D) (60), and then attended a late-afternoon laboratory session in which they were assessed for weight, height, and blood pressure, and provided a 20-mL venipuncture blood sample under resting conditions. Age, sex, race/ethnicity, smoking history, alcohol consumption, and 2-wk history of 13 minor illness symptoms (e.g., headache, upset stomach) were assessed as potential confounders. Unless otherwise indicated, all statistical results derive from generalized linear model analyses (61). All study procedures were approved by the institutional review board of the University of North Carolina at Chapel Hill.

Transcriptome Analysis. Genome-wide transcriptional profiling was carried out on isolated PBMCs from all 80 participants who provided blood samples. Assays were conducted as previously described (36, 62), with PBMCs isolated by density gradient centrifugation and total RNA extracted (RNeasy; Qiagen), tested for suitable mass (Nanodrop ND1000) and integrity (Bioanalyzer; Agilent), and converted to fluorescent cRNA for hybridization to Illumina Human HT-12 v4 BeadArrays following the manufacturer's standard protocol in the University of California, Los Angeles, Neuroscience Genomics Core Laboratory. Quantile-normalized gene expression values (Gene Expression Omnibus series GSE45330) were transformed to $\log_2$ for general linear model analyses quantifying association of transcript abundance with continuous (*z*-score) measures of hedonic and eudaimonic well-being (each controlling for the other) while also controlling for age, sex, race/ethnicity, BMI, alcohol consumption, smoking, and minor illness symptoms. To ensure that results were not confounded by individual differences in the prevalence of specific leukocyte subtypes within the PBMC pool (63), analyses also controlled for the prevalence of transcripts marking T lymphocyte subsets (*CD3D*, *CD3E*, *CD4*, *CD8A*), B lymphocytes (*CD19*), natural killer cells (CD16/*FCGR3A*, *CD56*/NCAM1), and monocytes (*CD14*) (64). Primary analyses focused on an a priori-defined contrast score representing the CTRA profile of up-regulated expression of proinflammatory genes (*IL1A*, *IL1B*, *IL6*, *IL8*, *TNF*, *PTGS1*, *PTGS2*, *FOS*, *FOSB*, *FOSL1*, *FOSL2*, *JUN*, *JUNB*, *JUND*, *NFKB1*, *NFKB2*, *REL*, *RELA*, and *RELB*) and down-regulated expression of genes involved in type I IFN responses (*GBP1*, *IFI16*, *IFI27*, *IFI27L1-2*, *IFI30*, *IFI35*, *IFI44*, *IFI44L*, *IFI6*, *IFIH1*, *IFIT1-3*, *IFIT5*, *IFIT1L*, *IFITM1-3*, *IFITM4P*, *IFITM5*, *IFNB1*, *IRF2*, *IRF7-8*, *MX1-2*, *OAS1-3*, and *OASL*) and antibody synthesis (*IGJ*, *IGLL1*, and *IGLL3*) (12, 33). To identify transcription control pathways that may mediate observed transcriptional differences, initial "low-level" genome-wide analyses identified all transcripts showing a point estimate of ≥1.5-fold differential expression across the range −2 SD to +2 SD relative to mean levels of eudaimonic and hedonic well-being (each adjusted for the other and for the covariates listed earlier), and those putatively associated genes were subject to TELiS promoter-based bioinformatic analysis (40) to assess activity of NF-κB, AP-1, IRF, and STAT family transcription factors previously linked to CTRA transcriptional dynamics (TRANSFAC V$CREL_01, V$AP1_Q4, V$IRF1_01, V$IRF2_01, V$STAT_01) (40), with results averaged over nine parametric variations of MatInspector scan stringency and promoter length (65). TOA was applied to the low-level association data to identify the specific PBMC subtypes mediating the observed differences in gene expression, as previously described (36). Low-level transcript-phenotype associations (Datasets S1 and S2) were estimated solely as inputs into high-level TELiS and TOA gene set expression analyses and are not tested for statistical reliability at the level of individual genes. Split-half replication studies and Monte Carlo power analyses were conducted to verify replicability of high-level associations of a priori-defined CTRA-related gene sets with phenotypes (*SI Methods* and Figs. S1–S7). Additional analytic details are provided in *SI Methods*.

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