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Optimism and the Conserved Transcriptional Response to Adversity

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Abstract

Dispositional optimism, a personality trait predisposing individuals to positive expectations, has been suggested to promote better health. However, little is known about the biological mechanism of the salubrious health effects associated with optimism. We hypothesized that by diminishing a sense of threat to the self, optimism will be associated with a healthier profile of gene expression in immune cells. Specifically, the "conserved transcriptional response to adversity" (CTRA) is activated by fight-or-flight stress responses and results in increased transcription of genes involved in inflammation and decreased transcription of genes involved in antiviral defense. In a sample of 114 male Japanese workers, we found that optimism was inversely linked to CTRA after controlling for age, BMI, and indices of well-being. These results are consistent with the hypothesis that reduced activity of threat-related gene expression programs may contribute to the health effects associated with optimism.

Keywords

optimism; biological health; conserved transcriptional response to adversity

1. Introduction

Dispositional optimism has been linked to better physical health (Carver, Scheier, & Segerstrom, 2010; Tindle et al., 2009). Most theoretical accounts for this relationship implicate behavioral mechanisms, such as optimism's effects on health-promoting behaviors (Allison et al., 2003; Carver et al., 2010), active coping (Fitzgerald et al., 1993; Nes & Segerstrom, 2006), and social support (Brissette et al., 2002). However, optimism may also have impacts on health at the biological level. Here, we explore one potential molecular

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mechanism for the health benefits of dispositional optimism, which may complement the extant psychological theories about behavioral mechanisms. This research draws on recent work in social genomics (Cole et al., 2015; Slavich & Cole, 2013), which has found that humans and other vertebrates activate a conserved pattern of gene transcriptional responses when they experience extended periods of threat or uncertainty. This molecular pattern, called the conserved transcriptional response to adversity (CTRA), is mediated by the sympathetic nervous system "fight-or-flight" response and is thought to have evolved to defend against physical injury during periods of heightened risk. The CTRA involves up-regulated transcription of genes involved in pro-inflammatory responses (such as *IL1B*, *IL8*, and *IL6*), which play a key role in immune responses to wounding injuries and related bacterial infections. It also involves a complementary down-regulation of antiviral genes (e.g., *IFI*- and *ISG*-family genes) and genes involved in antibody synthesis (e.g., *IGJ*). The CTRA supposedly evolved to fight against physical threats. However, among humans, it may also be triggered by non-physical threats, including threats to the symbolic self, such as social isolation (see Cole et al., 2007; Slavich & Cole, 2013).

CTRA activation has been observed in a variety of adverse life circumstances, such as social isolation, low socioeconomic status, bereavement, and chronic stress (Cole et al., 2007; Levine et al., 2017; O'Connor et al., 2014; Slavich & Cole, 2013). Conversely, psychosocial factors that mitigate perceived threat, such as finding meaning and purpose in life (Fredrickson et al., 2013) or in one's work (Kitayama et al., 2016), have been linked to reduced CTRA expression. We hypothesize that optimism may serve as another type of psychological resource that can mitigate the perceived likelihood or severity of threat, and thus down-regulate the CTRA. Optimistic people expect positive outcomes, and as a consequence, are likely to feel threatened less often and/or less severely than pessimists. This mechanism may also contribute to previously observed links between optimism and cellular immune parameters (Cohen et al., 1999; Ikeda et al., 2011). So far, however, no research has examined the relationship between dispositional optimism and CTRA. The present study examined this relationship after controlling for potential confounders such as demographic variables, health behavior risk factors, and other indices of general well-being (e.g., hedonic and eudaimonic well-being).

2. Material and Method

2.1. Participants

We used data reported in the Kitayama et al. (2016) study on the relationship between workplace experiences and leukocyte gene expression patterns in employees of a Japanese firm. One hundred fourteen Japanese male fulltime workers (age 39–63, Mean = 48) in a large Japanese IT firm (headquartered in Tokyo) participated. Only males were recruited because the great majority of the workers at the studied firm were men. They were tested during annual health check sessions run by the firm (conducted in Dec 2014). Any worker who came to the health check clinic was offered a chance to participate and provided a written consent form. Only those who agreed to complete the survey and provide blood samples were enrolled. Study procedures were approved by the Institutional Review Boards at Kyoto University and the University of California, Los Angeles. All procedures

contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

2.2. Procedure and Measures

Participants completed a packet of questionnaires that included our measure of optimism as well as measures of control variables, including demographic information, health-risk factors, and well-being. Participants' blood samples were then collected under a protocol previously reported in Kitayama et al. (2016).

2.2.1. Optimism.—We assessed dispositional optimism with a 6-item Life Orientation Test–Revised (LOT-R; Scheier, Carver, & Bridges, 1994; e.g., "In uncertain times, I usually expect the best"). Participants indicated their agreement with each statement using a 5-point scale (range 1–5). Three negative items were reverse-scored before being averaged to create a single index of optimism (α = .57, M = 3.17, SD = .51).

2.2.2. Control variables.—We controlled for several variables that might confound the relationship between optimism and CTRA, including demographic variables, health-risk factors, and well-being. Participants reported their age, annual household income (coded 1–9 with cut-points at 3, 4, 5, 6, 7, 10, 15, and 20 million yen), history of heavy alcohol consumption (coded 1 = three or more drinks/day, 0 = two or fewer drinks/day), history of smoking (1 = present, 0 = absent). Weight and height were assessed by clinic staff members and used to calculate body mass index (BMI) (kg/m^2).

We also controlled for two general well-being indices, hedonic and eudaimonic well-being, which were previously linked to CTRA (Fredrickson et al., 2013; Kitayama et al., 2016). Participants used a 6-point scale (0 = *never*, 5= *everyday*) to rate their levels of hedonic well-being within the past 30 days (3-items; e.g. "how often did you feel happy?"; α = .89, M = 2.27, SD = 1.03) and eudaimonic well-being (11-items; e.g., "How often did you feel that your life has a sense of direction or meaning to it?"; α = .84, M = 1.91, SD = .87; Keyes, 2014; Lamers et al., 2011).

2.2.3. Blood draw and CTRA gene expression.—Blood samples were collected by antecubital venipuncture into PAXgene RNA tubes and stored at −20℃. Samples were shipped to the UCLA Social Genomics Core Laboratory, where RNA was extracted (Qiagen QIAcube), tested for suitable mass (Nanodrop ND1000) and integrity (Agilent TapeStation), converted to fluorescent cRNA (Ambion TotalPrep), and hybridized to Illumina Human HT-12 v4 BeadArrays, following the manufacturer's standard protocol. Gene expression levels were assessed in peripheral blood samples using microarray-based transcriptome profiling, as previously described (Kitayama et al., 2016). Briefly RNA was extracted from whole blood samples (PAXgene RNA tubes) and assayed for the expression of mRNA from all named human genes using Illumina HT-12 microarrays (see Kitayama et al., 2016 for more details).

2.2.4. Analytic strategy.—Gene expression values (quantile-normalized, log2-transformed, and mean-centered by gene) were analyzed by linear models to quantify the

magnitude of association between *z*-score standardized optimism scores and an a priori-specified CTRA composite score computed over 53 indicator genes (Fredrickson et al., 2013), with 19 pro-inflammatory genes weighted +1 and 34 antiviral and antibody-related genes weighted −1 (to reflect their inverse relationship to the CTRA profile).

We tested our prediction by performing a series of regression analyses. Our benchmark analysis (Model 1) tested the association of optimism with CTRA while controlling for standard demographic variables (age and income) and health-risk factors (alcohol consumption, smoking history, and BMI) as in the previous work (see Kitayama et al., 2016 for the same approach). Several ancillary analyses were also conducted, including: Model 0, which was a simple association analysis not controlling for any covariates; Model 2, which added to Model 1 measures of eudaimonic and hedonic well-being in order to test the unique effect of optimism on CTRA outside of general well-being and positive emotional states; and Model 3, which added to Model 2 mRNA prevalence for 8 gene transcripts that mark major leukocyte subsets, including NK cells (CD16/*FCGR3A*, CD56/*NCAM1*), CD4+ and CD8+ T cells (*CD3D*, *CD3E*, *CD4*, *CD8A*), and monocytes (*CD14*) (see Kitayama et al., 2016 for the same approach). Bootstrap resampling of linear model residual vectors was used to estimate the standard error of the average association coefficient across the 53 CTRA indicator genes (i.e., controlling for their intercorrelations).

3. Results

We examined the relationship between dispositional optimism and CTRA gene expression. As predicted, the analysis controlling for demographic characteristics and health-risk factors (Model 1) showed that individual differences in optimism were inversely associated with CTRA gene expression ($b = -.048 \pm$ SE, .017 log2 gene expression units per SD optimism, $p = .0053$; see Figure 1)[1]. The magnitude of this association was such that a hypothetical individual with a high level of optimism (z = +2) is estimated to show a 12.5% reduction in the average expression of 53 CTRA indicator genes relative to a hypothetical individual with low levels of optimism (z = −2). Similar effects were observed in a simple association analysis that did not control for any covariates (Model 0: $b = -.046 \pm .016$, $p = .0059$).

As previously reported (Kitayama et al, 2016), general eudaimonic well-being was related to lower CTRA gene expression whereas general hedonic well-being was related to higher CTRA gene expression in this sample. To determine whether trait optimism had a distinct relationship to CTRA gene expression beyond what is attributable to individual variations in these two dimensions of general well-being, Model 2 additionally controlled for both eudaimonic and hedonic well-being scores. The effect of optimism remained statistically significant (residual optimism association: $b = -.039 \pm .016$, $p = .0198$; see Figure 1). The association between optimism and CTRA gene expression also remained significant when Model 3 analysis controlled for variations in leukocyte subset prevalence as indicated by mRNA's encoding major leukocyte subset markers ($b = -.049 \pm .016$, $p = .0038$).

[1]When optimism and pessimism items (αs = .60 and .52, respectively) were treated as separate predictors in separate models, both optimistic items ($b = -.036 \pm .016$, $p = .0328$) and pessimistic items ($b = +.037 \pm .016$, $p = .0252$) significantly predicted CTRA gene expression in the expected directions.

4. Discussion

Consistent with the hypothesis that trait optimism may buffer against threat-related biological responses, the present data link dispositional optimism to lower expression of the CTRA transcriptome profile. This effect was independent of other health-risk factors (BMI, smoking, and alcohol consumption), demographic characteristics, generalized well-being and positive affect, and variations in leukocyte subset prevalence. These data suggest that reduced CTRA gene expression may represent one potential molecular mechanism that could contribute to the health benefits of dispositional optimism and may thereby complement the behavioral pathways previously implicated (Carver et al., 2010).

Our finding is consistent with previous evidence linking positive psychological factors to reduced CTRA activity (Fredrickson et al., 2013; Kitayama et al., 2016; Kohrt et al., 2016; Nelson-Coffey et al., 2017). Our data extend this literature by documenting a distinct role for dispositional optimism that is not captured by measures of eudaimonic or hedonic well-being. However, both relationships are consistent with the hypothesis that leukocyte gene regulation is shaped in part by psychological processes that affect people's perceptions of threat in their life circumstances. These observations suggest new opportunities for psychological interventions to help reduce CTRA gene expression (Nelson-Coffey et al., 2017).

Although our data are consistent with the main effect of dispositional optimism on CTRA in general (i.e., across a wide range of situations, due to differential probability that any given situation is perceived as threatening), some previous studies also find "stress-buffering" effects, wherein the effect of optimism is more pronounced for those facing objective, chronic, or complex stressors (Segerstrom, 2005, 2006). We were not able to assess such effects in this study because our sample was a relatively healthy community sample of workers not confronting any substantial or discrete stressor. Future research involving more heterogenous stress exposures will be required to assess potential buffering effects of optimism on CTRA gene expression.

There are limitations to this study, which need to be acknowledged. First, our work is cross-sectional and it remains possible that leukocyte gene expression might potentially influence optimism. Future studies will also be needed to assess the generalizability of these results beyond the middle-aged Japanese male workers. Other factors (i.e., gender, age, culture, stressor exposure, chronicity, or complexity) might moderate the relationship between optimism and CTRA (although we have no theoretical reason to expect such moderation for demographic or cultural variables). Finally, this study provides no information on the biological pathways through which optimism might be transduced into changes in leukocyte gene expression. However, these results do join previous research on other immunological outcomes in suggesting that optimism may affect health in part by influencing host resistance to disease at the biological level.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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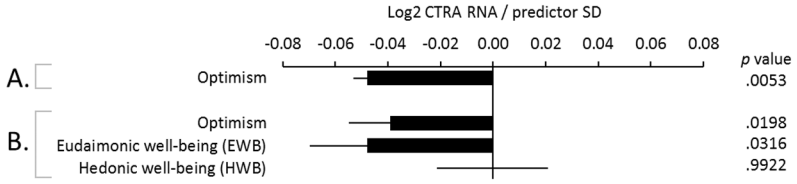

Figure 1.

Relationship between optimism and CTRA gene expression to optimism in Model 1 (upper) and Model 2 (lower). Model 1 controlled for age, income, smoking status, alcohol consumption, and BMI, and Model 2 additionally controlled for eudaimonic and hedonic well-being scores.