Kindness in the blood: A randomized controlled trial of the gene regulatory impact of prosocial behavior

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ABSTRACT

Context: Prosocial behavior is linked to longevity, but few studies have experimentally manipulated prosocial behavior to identify the causal mechanisms underlying this association. One possible mediating pathway involves changes in gene expression that may subsequently influence disease development or resistance.
Design, setting, participants: In the current study, we examined changes in a leukocyte gene expression profile known as the Conserved Transcriptional Response to Adversity (CTRA) in 159 adults who were randomly assigned for 4 weeks to engage in prosocial behavior directed towards specific others, prosocial behavior directed towards the world in general, self-focused kindness, or a neutral control task.
Results: Those randomized to prosocial behavior towards specific others demonstrated improvements (i.e., reductions) in leukocyte expression of CTRA indicator genes. No significant changes in CTRA gene expression were observed in the other 3 conditions.
Conclusion: These findings suggest that prosocial behavior can causally impact leukocyte gene expression profiles in ways that might potentially help explain the previously observed health advantages associated with social ties.

1. Introduction

Conventional wisdom touts the benefits of "treating yourself" as a means of maintaining psychological and physical health. Media, advertising, and other popular culture sources reinforce the idea that pampering oneself can lead to increased subjective well-being, reduced stress, and bolstered physical health. Despite these popular notions, however, empirical evidence suggests that prosocial, rather than self-focused, behavior is linked with positive health outcomes (Brown et al., 2003, 2009; Brown and Brown, 2015; Burr et al., 2016; Konrath et al., 2012). Given the strong links between prosocial behavior and broad, long-term physical health outcomes (i.e., cardiovascular disease risk, mortality), surprisingly few studies have experimentally tested whether increasing prosocial behavior leads to improvements in biological processes that may potentially mediate these long-term outcomes. Furthermore, no research has compared the potential effects of prosocial versus self-focused behaviors on such indicators. In the present study, we examine changes in pro-inflammatory and antiviral gene expression in response to experimentally induced prosocial behavior versus self-focused behavior.

1.1. Prosocial behavior

Prosocial behavior involves voluntary acts performed with the intention of benefitting others (Penner et al., 2005) and is hypothesized to represent the key individual-level process underlying the development of human social systems (Churchland, 2011; Wilson, 2012). Prosocial behavior can include acts directed at a specific other, such as purchasing coffee for a stranger, or individual efforts to better the world that are not directed at any specific individual, such as picking up litter. Beyond the general effects of social ties, observational epidemiology has also documented several health correlates of prosocial behavior in particular, including reduced risk of cardiovascular disease and mortality (Brown et al., 2003, 2009; Konrath et al., 2012; Poulin and Holman, 2013). These effects have been hypothesized to stem from neurophysiological correlates of prosocial behavior such as alterations in oxytocin and progesterone activity (Brown and Brown, 2015) or altered activity of the hypothalamus-pituitary-adrenal axis and sympathetic nervous system (Eisenberger and Cole, 2012). However, the observational epidemiological studies cannot rule out the possibility that associations between prosocial behavior and health arise from

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reverse causation (e.g., healthier people being more able or inclined to provide assistance to others).

Prosocial behavior can be experimentally manipulated by instructing participants to practice weekly acts of kindness (Layous et al., 2012; Nelson et al., 2016; Weinstein and Ryan, 2010). These studies have documented numerous social benefits of prosocial behavior, including improved social and career skills, social integration, peer acceptance, reciprocity, and social adjustment, as well as favorable psychological outcomes such as increased happiness and psychological flourishing (Crick, 1996; Layous et al., 2012; Nelson et al., 2016; Penner et al., 2005). However, the impact of such manipulations on health-relevant biological processes has not yet been examined.

1.2. Self-focused behavior and health

One theoretical question that remains to be clarified regards the distinction between producing positive behavior (i.e., a positive intention to benefit) vs. its prosocial nature (i.e., an intention to benefit others). Indeed, it is conceivable that directing positive behavior toward the self might also affect health, either by reducing stress-related processes or through incidental alteration of physiological processes by positive practices. For example, self-focused positive behaviors such as consuming dark chocolate, cocoa, or red wine have been shown to decrease markers of inflammation (Katz et al., 2011; Nicod et al., 2014). Favorable effects on inflammation and immune regulation have also been documented for napping (Faraut et al., 2015), having a sauna session (Pilch et al., 2013), and receiving regular massages (Rapaport et al., 2012). To distinguish the effects of producing positive behavior per se from the effects of its prosocial impact, this study contrasted the effects of positive behaviors directed at the self vs. others.

1.4. Human Social Genomics

Research has begun to map the molecular pathways through which negative social and psychological processes can influence disease risk by altering the pattern of gene expression by the human genome (Cole, 2014; Slavich and Cole, 2013). This research has identified a conserved transcriptional response to adversity (CTRA) in circulating leukocytes that is characterized by up-regulation of pro-inflammatory genes and down-regulation of genes involved in innate antiviral responses and antibody production (Cole, 2014; Slavich and Cole, 2013). The CTRA gene expression profile is mediated by both per-cell alterations in gene transcription and increased production of specific subtypes of leukocytes (particularly myeloid lineage monocytes and dendritic cells; Cole et al., 2011; Cole, 2014; Powell et al., 2013; Slavich and Cole, 2013). These dynamics are mediated by activation of β-adrenergic signaling pathways in response to sympathetic nervous system activity and take place over the course of several hours to a few days (Cole, 2010, 2014; Cole et al., 2015a; Powell et al., 2013; Slavich and Cole, 2013).

The leukocyte CTRA represents one molecular process that may potentially mediate the health effects of negative psychological processes and adverse social conditions (Cole et al., 2007, 2011, 2015a, 2015b). Little is known about how positive psychological processes may impact the CTRA, although several studies have found down-regulation of the CTRA in people with high levels of eudaimonic well-being (a multi-faceted complex of self-transcendent aspects of well-being, including purpose in life, positive relations with others, and several other prosocial components; Cole et al., 2015b; Fredrickson et al 2013, 2015; Kitayama et al 2016). However, all of the results involving eudaimonic well-being come from cross-sectional studies, and it remains unclear whether there is any causal effect of eudaimonic well-being on CTRA gene expression or whether any such effects stem specifically from the prosocial components of eudaimonia.

1.3. Current study

To clarify the molecular pathways that link prosocial behavior to human health, this study examined changes in leukocyte CTRA profiles in response to the experimental manipulation of prosocial behavior over a 5-week longitudinal study. Two forms of prosocial behavior – acts of kindness directed toward another individual and acts of kindness directed toward the world or humanity at large – were contrasted with self-focused positive behavior (acts of kindness directed toward oneself) and a neutral control condition.

2. Method

Participants (N = 159; 77.4% female) were recruited in 2015 from a community sample of adults in Southern California in exchange for $100. A plurality of participants were white (42.8%), followed by Hispanic/Latino(a) (23.3%), other or more than one (11.3%), Asian (9.4%), Black/African American (9.4%), Middle Eastern (1.9%), and Hawaiian/Pacific Islander (1.3%). One participant declined to provide ethnic or racial information. Participants' ages ranged from 23 to 93 (M_{age} = 38.52; SD = 12.73). Rates of attrition were low (n = 7 dropouts) and did not differ significantly across conditions, χ^2(3) = 6.33, p = .097, although there was a trend toward higher rates of attrition in the *kindness-to-world* condition (n = 5, compared to n = 0, 1, and 1 in *control*, *kindness-to-self*, and *kindness-to-other* conditions, respectively; see Fig. 1 for CONSORT diagram and Supplemental materials for CONSORT checklist). Participants who dropped out of the study did not differ significantly on any of the demographic factors or variables of interest. Participants who provided blood samples at both baseline and post-test were included in genomic analyses. Prior to data collection, we decided to recruit approximately 160 participants (approximately 40 per group), which would provide adequate power (90%) to detect a large (1 SD) difference between two groups in the magnitude of change over time in average expression of the 53 a priori-specified CTRA indicator genes (see below for additional analytic details). Data collection continued until all participants completed the study.

2.1. Procedure

Participants volunteered to participate in a study involving positive activities and health. All participants came to the laboratory for the first and fifth time points (see Fig. 2 for study timeline). During the first time point (Week 1), participants gave consent, completed baseline measures, provided baseline dried blood spots (DBS; see Measures below), and were randomly assigned to one of four conditions: to perform acts of kindness for others (*kindness-to-others;* n = 33), to perform acts of kindness for the world in general (*kindness-to-world*; n = 48), to perform acts of kindness for themselves (*kindness-to-self*; n = 43), or to complete a neutral control activity (*control*; n = 35). Random assignment to condition was completed within Qualtrics, an online survey platform, and both participants and researchers were blind to condition. Supplemental materials contain full instructions and sample responses from each condition. Participants were asked to perform their assigned activities weekly for 4 weeks after baseline. At the second (Week 2), third (Week 3), and fourth (Week 4) time points, participants completed study measures and reported on the activities they performed. At the fifth time point (Week 5), participants returned to the laboratory to complete post-intervention measures (including a report of their activities) and to provide post-intervention DBS samples.

2.2. Coding

Each week, participants were prompted to list their acts relevant to their assigned conditions. Three independent judges read the participants' responses in the three kindness conditions to determine whether participants adhered to their assigned activities, indicating the number
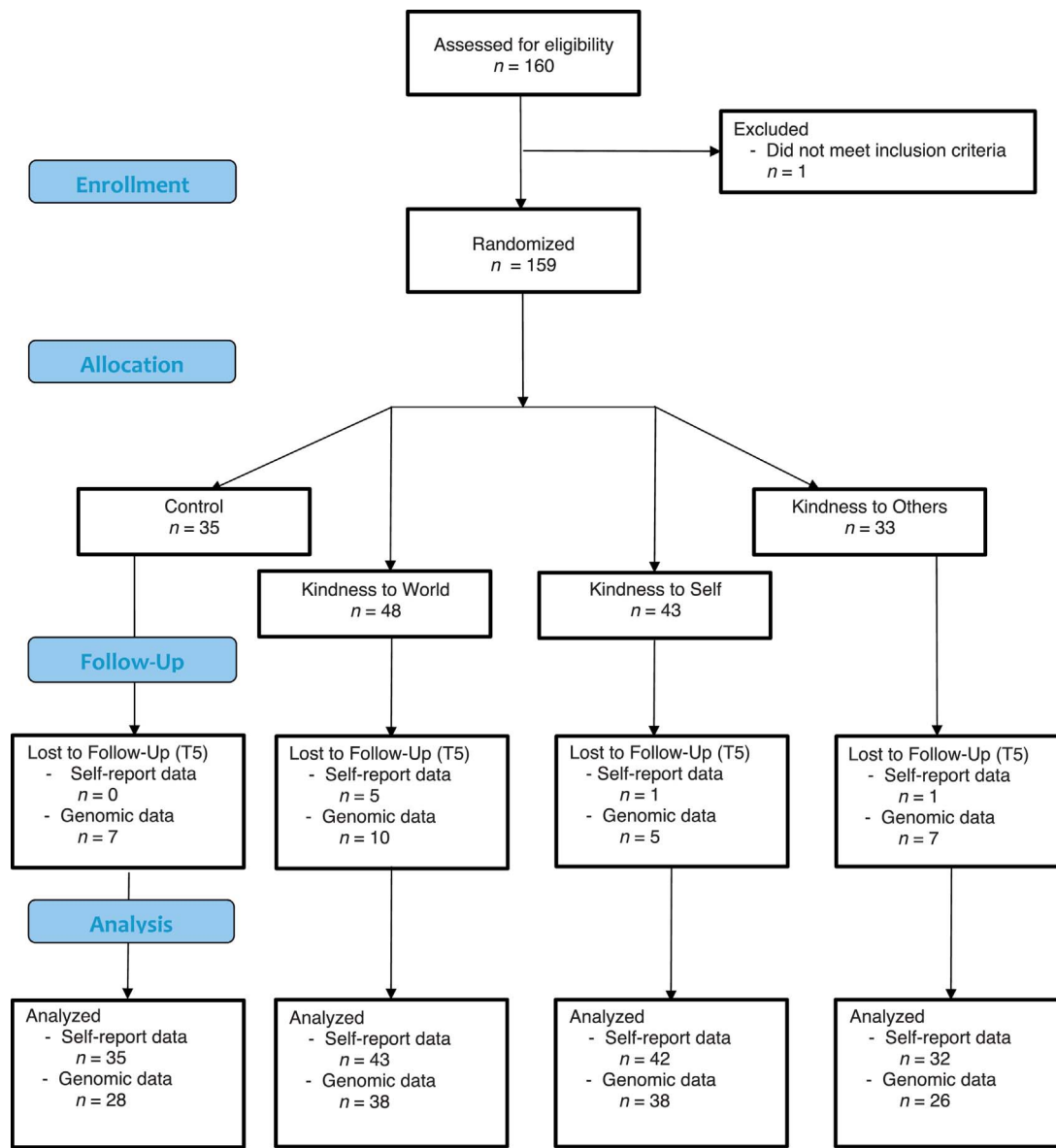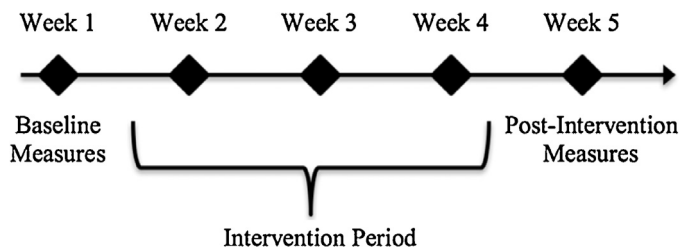
Fig. 1. CONSORT Diagram.

Fig. 2. Study timeline.

of acts each participant performed (ranging from 0 to 3). Across time points, reliability was high: intraclass correlation coefficients (ICCs: 2, 1) > .98. Participants largely adhered to instructions and completed their activities, with the average number of kind acts ranging from 2.62 to 2.77 across time points and no significant differences between conditions at each time point $Fs < 2.61$, $ps > .07$.

2.3. CTRA gene expression

Expression of CTRA indicator genes was assessed by genome-wide transcriptional profiling of DBS RNA samples collected at baseline and Week 5 (post-intervention). Procedures followed those of previous DBS transcriptome profiling studies (Kohrt et al., 2016; McDade et al., 2016), with blood collected onto Whatman filter papers via lancet finger prick, air-dried at room temperature, and stored prior to analysis in zip-lock plastic bags with a desiccant pack. RNA extraction and genome-wide transcriptional profiling were conducted as previously described (Kohrt et al., 2016; McDade et al., 2016), using Qiagen RNEasy reagents for RNA extraction, the NuGEN Ovation PicoSL WTA System for reverse transcription of RNA into complementary DNA, the NuGEN Encore BiotinIL Module for fluorescent target sample synthesis, and Illumina Human HT-12 v4.0 BeadChips for genome-wide transcriptome profiling in the UCLA Neuroscience Genomics Core, all following the manufacturers' standard protocols. Routine post-assay data quality assurance procedures identified 26 samples with suboptimal global validity (25th percentile of probe florescence intensity distribution < 80 intensity units), and these samples were deleted from all subsequent analyses.

Table 1
Sample Characteristics.

	Control	Kindness-to-other	Kindness-to-self	Kindness-to-world	p^*
Age (mean ± SD years)	39 ± 14	41 ± 16	39 ± 13	36 ± 10	.4852
Sex (% Female)	75%	73%	79%	79%	.9296
Smoking history (%)	0%	0%	0%	0%	–
Heavy alcohol history (%)	0%	0%	0%	0%	–
Race/ethnicity (% self-identified)					.8573
White	43%	38%	47%	42%	
Black	7%	19%	8%	8%	
Hispanic	21%	19%	21%	29%	
Asian	18%	8%	11%	5%	
Other	11%	15%	13%	16%	
Baseline URI symptoms (mean ± SD)	1.8 ± 0.7	1.9 ± 0.9	1.6 ± 0.6	1.6 ± 0.6	.3379
Follow-up URI symptoms (mean ± SD)	1.5 ± 0.6	1.6 ± 0.8	1.3 ± 0.3	1.3 ± 0.3	.1210

* Omnibus test statistic from ANOVA (continuous variables) or X^2 (categorical variables).

2.4. Analysis

Transcriptome data analysis followed methods employed and validated in previous research (Kohrt et al., 2016; McDade et al., 2016). Briefly, raw gene expression data were quantile-normalized (to remove technical variations across samples), $\log_2$ transformed (to stabilize biological variance over the range of observed gene expression values), and z-score standardized within gene (to stabilize the > 10-fold difference in variance across genes). For each gene, we computed the intra-individual change in its quantitative expression level from baseline to post-intervention follow-up, and we used mixed effect linear models (SAS PROC MIXED) to analyze group differences in the magnitude of change over time.

Analyses focused on an a priori-defined set of 53 CTRA indicator genes used in previous studies (Cole et al., 2015b; Fredrickson et al., 2013, 2015), 36 of which were reliably detectable across this study's DBS samples (i.e., quantified at above-background level in all valid samples by Illumina GenomeStudio software). (DBS samples yield small quantities of RNA, rendering it difficult to uniformly detect some genes that are expressed at relatively low levels or inconsistently across individuals; Kohrt et al., 2016; McDade et al., 2016.) The 36 transcripts available for analysis included 13 pro-inflammatory genes (*FOS, FOSL1-2, IL1A, JUN, JUNB, NFKB1-2, PTGS2, REL, RELA, RELB, TNF*), 21 genes involved in Type I interferon response (*GBP1, IFI27, IFI27L1-2, IFI30, IFI35, IFI44L, IFI6, IFIH1, IFIT1-3, IFIT1L, IFITM2, IFITM4P, IRF2, IRF7-8, MX1, OAS1-2, OASL*), and 2 genes involved in antibody synthesis (*IGJ, IGLL1*). (The 17 genes unavailable for analysis due to missing values were *FOSB, IFI16, IFI44, IFIT2, IFIT5, IFITM1, IFITM3, IFITM5, IFNB1, IGLL3, IL1B, IL6, IL8, JUND, MX2, OAS3,* and *PTGS1*.) Gene-specific z-score signs were reversed for the antiviral and antibody-related gene sets to reflect their inverse relationship to the overall CTRA profile (Cole et al., 2015b; Fredrickson et al., 2013, 2015).

Mixed models were estimated by maximum likelihood and utilized an unstructured covariance matrix to account for any residual heteroscedasticity and correlation among residuals across genes. Primary analyses examined group differences in the average magnitude of change over time using a single-factor main effect analysis. Secondary covariate-adjusted analyses controlled for effects of age (coded continuously in years), sex (1/0), a four-category race/ethnicity variable (1/0 indicators for African-American, Asian-American, Hispanic, and Other Non-Caucasian ethnicity, with Caucasian serving as the reference category), current illness symptoms (average of 1–5 ratings of current nasal congestion, muscle aches, upset stomach, hot/cold spells, poor appetite, coughing/sore throat), and relative composition of the DBS leukocyte pool by monocytes, CD4+ and CD8+ T lymphocytes, B lymphocytes, and Natural Killer cells, as indicated by the relative abundance of gene transcripts encoding 8 canonical markers of these cell types (*CD14, CD3D, CD3E, CD4, CD8A, CD19, FCGR3A*/CD16, *NCAM1*/CD56). History of smoking and heavy alcohol consumption

were also assessed as potential covariates, but no participants reported either of these.

All valid outcome data were included in analyses, regardless of whether or how completely participants complied with the instructions of their experimental condition. The only criteria for excluding data from analysis involved *a priori*-specified metrics for the technical invalidity of outcome values (i.e., individual data points declared missing or invalid by Illumina GenomeStudio image processing software or an entire sample declared invalid based on 25th percentile fluorescence intensity < 80 units) or absence of a baseline or follow-up DBS sample (in which case no change scores could be computed). No statistical testing was performed at the level of individual genes because our substantive interest lay only in the average expression level across all available CTRA indicator transcripts, and previous analytic studies show gene-specific statistical testing to be substantially less reliable than analysis of gene set averages (Fredrickson et al., 2013).

A total of 314 dried blood spot samples were collected. After removing samples that were unusable due to study attrition (i.e., no post-intervention paired sample, $n = 4$) or insufficient RNA input (i.e., blood spot too small, $n = 26$ paired samples), a total of 130 pairs of dried blood spot samples were analyzed.

3. Results

3.1. Sample characteristics

Characteristics of this community-dwelling adult study sample are reported in Table 1. As expected in a randomized experiment, *kindness-to-other*, *kindness-to-world*, *kindness-to-self*, and *control* groups did not differ in average age, sex, race/ethnicity, or current illness symptoms.

3.2. Effects of prosocial behavior on CTRA gene expression

Fig. 2 depicts the study timeline. Groups did not differ in baseline level of CTRA gene expression (omnibus $F(3, 126) = 0.53$, $p = .66$). However, groups did differ significantly in the relative magnitude of change in CTRA gene expression from baseline to the Week 5 post-study follow-up (omnibus $F(3, 126) = 3.96$, $p = .01$). Group-specific parameters showed that participants in the *kindness-to-others* condition showed a greater decrease over time in CTRA gene expression than did those in the *control* group, $\beta = -.098$, $t(126) = -2.44$, $p = .02$ (Fig. 3; Supplemental Table 1A). However, CTRA change over time did not differ from the *control* group for those in the *kindness-to-world* condition, $\beta = -.004$, $t(126) = -0.12$, $p = .91$, or the *kindness-to-self* condition, $\beta = .028$, $t(126) = 0.76$, $p = .45$.

In analyses of absolute change over time (i.e., nested within group), the *kindness-to-others* condition induced a significant decrease in CTRA gene expression over time, $\beta = -.085$, $t(126) = -2.94$, $p = .004$ (see also Supplemental Table 1B). However, no significant change over time
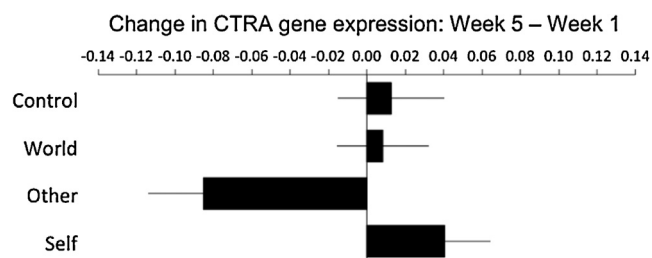
Change in CTRA gene expression: Week 5 – Week 1

Fig. 3. Change in CTRA gene expression. Data represent mean (± SE) change from baseline to post-intervention follow-up in average expression of 36 CTRA indicator genes. Units are mean of 36 z-transformed values of log2 gene expression levels.

was observed for the *kindness-to-world* condition, β = .008, $t(126)$ = 0.35, p = .73. The change in CTRA gene expression over time was also significantly greater for the *kindness-to-others* condition than for the *kindness-to-world* condition, β = −.093, $t(126)$ = −2.49, p = .014. No significant change over time was observed for the *control* condition, β = .013, $t(126)$ = 0.46, p = .65, and the *kindness-to-self* condition showed a weak (nonsignificant) trend toward increased CTRA gene expression over time, β = .041, $t(126)$ = 1.69, p = .09.

Similar results emerged in secondary analyses that controlled for individual differences in age, sex, race/ethnicity, current illness symptoms, and 8 RNA indicators of major leukocyte subsets (monocytes, CD4+ and CD8+ T cells, B cells, and NK cells). Again groups differed significantly in CTRA change over time, $F(3, 110)$ = 3.36, p = .02, and only the *kindness-to-others* condition showed a significant difference from the control group, β = −.109, $t(110)$ = 2.76, p = .007.

Participants in the *kindness-to-others* condition showed non-significant trends towards greater reductions in negative affect and greater increases in perceived connectedness compared to the control group (see Supplemental Table 3, Figs. 2 and 3). However, the *kindness-to-others* condition continued to show significantly greater reductions in CTRA expression compared to other groups in analyses controlling for differential changes in negative affect and connectedness (omnibus $F(3, 122)$ = 4.08, p = .009).

4. Discussion

In this randomized controlled experiment with a diverse community sample of participants, engagement in prosocial behavior led to reduced expression of CTRA indicator genes. These findings demonstrate a causal effect of prosocial behavior on leukocyte gene regulation, and they contribute to a growing body of literature mapping the molecular pathways that may link prosocial behavior to physical health. These findings also add purposeful engagement in prosocial behavior to the small list of other interventions that have previously been found to reduce CTRA gene expression (e.g., meditation, yoga, and cognitive-behavioral stress management; Antoni et al., 2012; Black et al., 2013; Bower et al., 2014; Creswell et al., 2012; Irwin et al., 2014).

4.1. Genomic benefits of prosocial behavior

The present study's findings are notable in light of the fact that this community sample was not selected for any degree of psychological threat or social disadvantage at baseline. Thus, relatively small increases in prosocial behavior are sufficient to reduce CTRA gene expression under basal conditions. No costly, instructor-led, or labor-intensive activities were required; simply incorporating small acts of kindness toward others into daily routines was sufficient to alter leukocyte gene regulation. However, it is important to note that the duration of these effects and their downstream impact on health remain to be established in future studies (see Limitations for additional discussion).

The present findings are also consistent with literature that links

prosocial behavior to favorable social outcomes such as peer acceptance (Layous et al., 2012), feelings of connectedness (Nelson et al., 2015), social adjustment (Crick, 1996), and eudaimonic well-being (Nelson et al., 2016), as well as to favorable health correlates including cardiovascular function and decreased mortality (Brown et al., 2003, 2009). Our findings extend that literature by providing the first experimental evidence that prosocial behavior can causally impact CTRA gene expression.

4.2. Psychobiological mechanisms

Although the present findings indicate a causal effect of prosocial behavior on CTRA gene expression, it remains to be determined how these effects are mediated physiologically and psychologically. Prosocial behavior has been theorized to directly modulate several neural and endocrine signaling pathways that might potentially modulate CTRA gene expression (Brown and Brown, 2015; Eisenberger and Cole, 2012). Prosocial behavior may also affect CTRA gene expression indirectly by promoting other social or psychological factors that have previously been linked to CTRA regulation, such as social connection, eudaimonic well-being, or reduced negative affect (Fredrickson et al 2013, 2015; Cole et al., 2007, 2011, 2015a, 2015b; Kitayama et al., 2016; Wingo and Gibson, 2015). In the present study, statistical control for differences in perceived connectedness and negative affect could not account for the effects of the kindness-to-others intervention on CTRA gene regulation. However, we do not yet know whether other more focal or robust measures of loneliness, emotional states, or eudaimonia might provide more sensitive indications of mediation. It also remains to be determined which neurobiological pathways mediate the effects of prosocial behavior. This is a particularly intriguing question in light of previous data showing that CTRA expression is biologically mediated in large part by threat-related systems (i.e., sympathetic nervous system/β-adrenergic signaling; Cole, 2014; Cole et al., 2015a; Powell et al., 2013). Defining the upstream neurobiological mediators in the CNS substrates of prosocial experience also remains an important topic for future research (Eisenberger and Cole, 2012).

4.3. Limitations and future directions

Although the present findings support the notion that prosocial behavior exerts favorable impacts on CTRA gene regulation, several important limitations should be noted. First, we only collected data on CTRA gene expression through 1 week post-intervention and it is unclear how long these effects might persist beyond the cessation of purposeful prosocial engagement. Future studies should include extended follow-up to assess the duration of these effects. Second, the health significance of the present genomic findings needs to be interpreted with caution until more is known about the quantitative relationship between CTRA gene expression and disease risk in healthy populations such as this one. Even though prosocial behavior causally influenced CTRA expression in this study, and CTRA expression has been linked elsewhere to clinical health outcomes (e.g., Antoni et al., 2016; Cole et al., 2015a; Knight et al., 2016), this study contains no measures of clinical health outcomes. In addition, although we postulate that our prosocial behavior intervention informs the understanding of the link between relationships and health, we did not directly measure whether our manipulation led to objective changes in participants' relationships. Future work examining relationship outcomes, such as improved relationship quality, in parallel with changes in gene expression, would be informative. Indeed, past evidence indicates that people are better liked by their peers after performing kind acts (Layous et al., 2012).

Finally, this study was designed to test a specific a priori hypothesis regarding a pre-specified set of CTRA indicator genes. This study was not designed or powered for genome-wide discovery analyses at the level of individual genes, and individual gene expression differences

were not tested for statistically significant association. Future studies using larger sample sizes may well reveal additional specific human gene transcripts that are modulated by prosocial behavior. In addition, our study also suffered from missing data on several CTRA indicator genes due to the limited RNA available from the DBS sampling method employed here. Although this limitation would not bias the validity of results for the indicator transcripts that do remain available, it does limit the generalizability of this study's results to other previous findings involving the full canonical 53-gene CTRA indicator profile.

4.4. Conclusion

In the present study, community-dwelling adults who were randomly assigned to perform prosocial acts – kind acts directed toward specific other individuals – showed significant declines in leukocyte CTRA gene expression over a 5-week period. These findings advance a small but promising area of research suggesting that purposefully engaging in positive activities over a relatively short period of time can positively impact biological processes. Indeed, our study provides the first indication that simply performing small acts of kindness for other individuals can impact human gene regulation.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2017.03.025.

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