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Full-length Article

An extraverted behavior intervention improves immune gene expression

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ABSTRACT

Background: Social connection is critical to both psychological well-being and optimal immune function. The present study tested whether a behavioral intervention to increase social connection (promoting extraverted behavior) might reduce a threat-related immunoregulatory gene expression program known as the Conserved Transcriptional Response to Adversity (CTRA). The CTRA is characterized by elevated inflammatory gene expression and reduced innate antiviral gene expression in response to beta adrenergic signaling and has been associated with adverse social conditions such as loneliness and ostracism.
Methods: In an 8-week intervention (with 6-week behavior change protocol), participants from a campus community (N = 119; 87 % undergraduate; 9 % graduate; 4 % staff) were randomized to act more extraverted (sociable; Extraversion condition) or track routine daily activities (Control condition). Participants reported on psychological outcomes and provided dried blood spots for RNA sampling at pre-test (Week 0), post-test (Week 8), and 1-month follow-up (Week 12). Multilevel models tested condition differences in CTRA expression over time and examined mediation via psychological outcomes.
Results: Pre-registered analyses of pre-specified CTRA indicator genes showed no significant effects. Secondary genome-wide bioinformatic analyses of NF-κB, IRF, and CREB transcription control pathways found significantly greater reductions in CTRA-characteristic gene regulation among the Extraversion group relative to controls. These effects were partially mediated by reductions in loneliness. However, the intervention effect on CTRA gene regulation was not sustained at 1-month follow-up.
Implications: Extraverted behavior may improve immune regulation by enhancing perceived social connection. Further research should replicate these findings and enhance the durability of effects.

1. Introduction

Social connection is vitally important for both psychological well-being (Baumeister & Leary, 1995; Ryan & Deci, 2000) and physical health (Hawkley & Cacioppo, 2010; Holt-Lunstad et al., 2015). In fact, the absence of social connection—loneliness—impacts a range of health outcomes, from mortality and cardiovascular disease to diabetes and infectious disease, and socially mediated alterations in immune function appear to contribute to these effects (Cole et al., 2015a; US Office of the Surgeon General, 2023). Given the biological risks associated with loneliness and social disconnection, there is great interest in identifying behavioral interventions that can reduce loneliness, enhance social connection, and thereby improve immune system function and health. One randomized controlled trial, for instance, found that mindfulness-based stress reduction could reduce both loneliness and inflammatory gene expression in parallel (Creswell et al., 2012). However, it has been challenging to identify behavioral interventions that can produce durable changes in social connection that are sufficiently robust to affect the immune system.

One potential approach to enhancing social connection is to simply ask people to act more sociable (extraverted). In interventions aimed at intentionally boosting extraverted behavior, people report greater psychological well-being as a result of acting more sociable (Margolis & Lyubomirsky, 2020; Van Allen et al., 2021). However, little is known about the impact of intentionally increased extraverted behavior on measures of physical health or immune function. In the present study, we sought to determine whether deliberately increasing extraverted behavior might produce durable improvements to social and psychological well-being (including reduced loneliness) and parallel reductions in inflammatory gene expression.

Our biological analyses focused on a pro-inflammatory gene regulation program known as the Conserved Transcriptional Response to

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Adversity (CTRA), which involves upregulated expression of pro-inflammatory genes (e.g., *IL1B, IL6, IL8, TNF*) and downregulated expression of innate antiviral genes (e.g., Type I interferons) in response to fight-or-flight/sympathetic nervous system signaling associated with social threat (Cole, 2014, 2019). Cross-sectional research has linked CTRA to a host of harmful social conditions, including loneliness (Cole et al., 2015b; Lee et al., 2023), adverse childhood experiences (Marie-Mitchell & Cole, 2022), discrimination (Thames et al., 2019), lower social well-being (i.e., reduced sense of belonging and acceptance; Fredrickson et al., 2015) and having a peripheral position within one's social network (Lee et al., 2023).

Longitudinal studies have also linked changes in CTRA gene expression to changes in loneliness (Cole et al., 2015a) and eudiamonic well-being (flourishing; Boyle et al., 2019). Further, two experimental studies found that engaging in prosocial behavior (acts of kindness) can reduce CTRA expression, and that these favorable biological effects persist at 1-week follow-up (Nelson-Coffey et al., 2017; Regan et al., 2022). However, it remains unknown whether intentionally enhancing sociable (extraverted) behavior might have similar effects in reducing CTRA gene expression and whether these biological effects endure beyond 1-week post-intervention.

The present randomized controlled study sought to determine: (1) whether intentionally increasing extraverted behavior over a 6-week period can reduce CTRA gene expression; (2) whether reductions in loneliness contribute to (mediate) the effects of the extraverted behavior intervention on CTRA expression (following analysis of significant intervention impacts on psychological outcomes; Martinez, 2025); and (3) whether the impact of extraverted behavior on CTRA persists 1 month following the sociability intervention. These questions were addressed as part of a larger set of pre-registered hypotheses (https://osf.io/g43p7/?view_only=1ea9fb9f1fe246ae9ce442b0bd5079ea), with other behavioral and psychological hypotheses not related to immune system gene regulation detailed elsewhere (Martinez, 2025).

2. Method

2.1. Participants

Participants ($N = 119$; $M_{age} = 21.51$, $SD = 6.56$; 78 % female; 46 % Hispanic/Latinx; 36 % Asian; 18 % White; 7 % Black/African American; 2 % Middle Eastern/North African; 1 % Native American/Alaskan Native; 2 % "Other" race) were recruited from the campus community (87 % undergraduate students; 9 % graduate students; 4 % staff) at the University of California, Riverside. Participants self-selected into a study advertised as one targeting social behavior but were advised at intake they may be asked to take part in a time tracking activity. All participants provided informed consent prior to their participation in the study. The study was approved by the Institutional Review Board at the University of California, Riverside, and is in accordance with the Declaration of Helsinki.

2.2. Procedure

As part of an 8-week extraverted behavior intervention (with 6-week behavior change protocol), participants completed a pre-test lab visit (Week 0) to complete self-report psychological outcomes and provide dried blood spots (DBS) for RNA sampling (DBS procedure further detailed below). After providing daily psychological measures during baseline week (Week 1), participants were randomized by Qualtrics' randomizer function to receive one of two study condition instructions during Week 2. Participants assigned to the Extraversion condition ($n = 59$; experimental condition) were instructed to act as "talkative, outgoing, and spontaneous" for 3 days a week of their choosing for the next 6 weeks. Participants in the Control condition ($n = 60$) were asked to keep track of their daily activities without changing their routines for 3 days a week of their choosing for the next 6 weeks. Both conditions received weekly online reminders about their condition instructions and returned to the lab at post-test (Week 8) and 1-month follow-up (Week 12) to complete psychological surveys and provide additional DBS samples. Participant retention is detailed in the CONSORT diagram (Fig. 1). Participants received up to $80 in compensation for completing all study timepoints. (See Martinez, 2025 for additional procedural details.).

DBS were sampled in a laboratory setting using Tasso-M20 devices applied to the upper bicep at pre-test, post-test, and 1-month follow-up. DBS samples were air dried and stored in zip-lock bags with desiccant packs. Following study completion, samples were transported to the UCLA Social Genomics Core Laboratory for RNA sequencing-based assay of CTRA gene expression from DBS as previously described (Snodgrass et al., 2022). RNA extraction, sequencing and related bioinformatic details are provided in the Appendix.

2.3. Measures

The following measures were assessed at pre-test (Week 0), post-test (Week 8), and 1-month follow-up (Week 12):

2.3.1. CTRA

CTRA was assessed in two ways (Cole, 2019). First, as pre-registered, the CTRA was assessed using a standard set of 53 indicator genes: 19 pro-inflammatory genes and 34 genes related to Type I Interferon response which were sign-inverted to reflect their inverse contribution to the CTRA profile (53-gene profile specified in Appendix; Cole et al., 2015a,b).

We also conducted a secondary analysis of CTRA gene regulation using a more complex measure based on signaling pathway bioinformatic analysis of genome-wide RNA correlates of experimentally induced change over time. Previous research finds this approach to show greater sensitivity compared to the pre-specified set of 53 CTRA indicator genes (Cole, 2019). This more complex genome-wide analyses first identifies all gene transcripts (genome-wide) that show 1.5-fold differential change over time in the intervention group v. controls (i.e., gene transcripts characterizing the Group × Time interaction), and then applies the TELiS promoter sequence-based bioinformatics analysis (Cole et al., 2005) to assess activity of the pro-inflammatory NF-κB transcription control pathway (which is upregulated in the context of the CTRA), the Interferon Response Factor pathway (IRF, which is downregulated in the context of the CTRA), and the CREB pathway that mediates sympathetic nervous system (fight-or-flight) signaling through the beta-adrenergic receptor system (which is known to mediate the effects of sympathetic activation on NF-κB and IRF activity). To the extent that the empirical transcriptional correlates of the Group × Time interaction are characterized by decreased NF-κB, increased IRF, and decreased CREB activity, the intervention's effects would be consistent with reduced CTRA activity as hypothesized.

2.3.2. Loneliness

Loneliness was measured using the 3-item loneliness subscale of the Comprehensive Inventory of Thriving (CIT; Su et al., 2014). Participants were asked to "indicate [their] agreement or disagreement with each of the following statements:" "I feel lonely," "I often feel left out," and "There is no one I feel close to," on a 1 ("strong disagree") to 5 ("strongly agree") Likert scale. No specific timeframe was indicated, consistent with the validated measure. The items were averaged to form a composite. The CIT loneliness subscale exhibited good internal consistency ($\alpha_{pre\text{-}test} = 0.75$; $\alpha_{post\text{-}test} = 0.75$; $\alpha_{follow\text{-}up} = 0.79$).

3. Analytic approach

3.1. Sample size

Target sample size (Total *N*: 108; 54 per condition) was determined

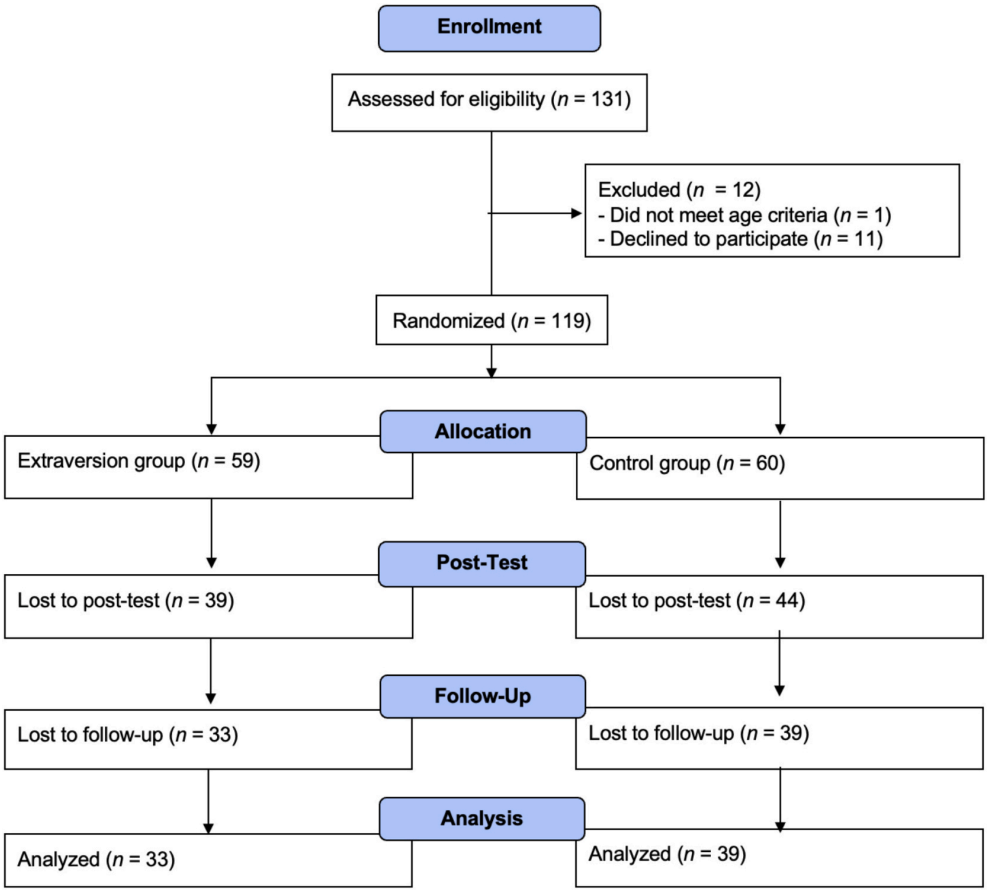

Fig. 1. CONSORT diagram. All available data from participants were used in analyses with use of maximum likelihood estimation. All biological samples were viable, and there were no case exclusions based on invalid mRNA data.

by estimating the total sample size required to detect a previously observed effect of $f = 0.25$ between extraverted behavior and positive affect with two groups and four measurement occasions at 90 % power (Margolis & Lyubomirsky, 2020). Our power analysis was based on a key psychological effect of interest (see Martinez, 2025), as there are no existing data regarding the effects of extraverted personality change on CTRA gene expression that would inform a specific power analysis to detect this effect.

3.2. Statistical approach

First, to test condition differences in pre- to post-intervention change in expression of the pre-registered 53 indicator gene measure of the CTRA, gene expression data were mean-centered within gene (to facilitate linear model estimation), and inverse indicator genes (interferon) were sign-inverted to reflect their inverse contribution to the CTRA. To account for the repeated measures design, data were analyzed using mixed effect linear models using the *nlme* package in R, with maximum likelihood estimation, and a random subject-specific intercept to control for correlation in linear model residuals across time and across the 53 CTRA indicator genes. Primary analysis models were unconditional (i.e., did not control for any additional covariates), with interpretation focusing on the single Group × Time interaction parameter that quantified group differences in the average change in CTRA indicator gene expression from pre- to post-intervention.

To determine whether controlling for known influences on CTRA gene expression might alter effects (e.g., by reducing the magnitude of unmodeled residual variation), secondary analyses controlled for age, sex, race, BMI, smoking, alcohol consumption, illness symptoms, and 8 mRNA transcripts indicating prevalence of major leukocyte subsets within the circulating cell pool (CD4+ and CD8+ T lymphocytes, B lymphocytes, natural killer cells, and monocytes). In all analyses of this hypothesis, the Group × Time interaction parameter quantifying group differences in change from baseline to post-intervention was the primary predictor of interest.

For the secondary analysis of CTRA gene expression using genome-wide analysis of transcription factor activity, the same unconditional (no covariates) Group × Time factorial analysis was used to estimate the magnitude of group difference in change over time for each gene (genome-wide), and all genes that showed >1.5-fold difference in change over time served as input into TELiS bioinformatics analysis assessing NF-κB, IRF and CREB activity (as previously detailed in Cole et al., 2005; Cole et al., 2020). Additional analytic details regarding this promoter sequence-based analysis are provided in the Appendix.

To determine whether the intervention continued to affect CTRA gene expression at 1-month follow-up, analyses were conducted as described above but focused instead on a second parameter in the Group × Time interaction—namely, the parameter quantifying group differences in change from pre-test to 1-month follow-up.

To determine whether changes in loneliness mediate the effects of intervention group on change in CTRA gene expression, analyses were conducted as described above with the addition of timepoint-specific loneliness measurements as a covariate. Conclusions were based on the extent to which statistical control for loneliness attenuated the

Group × Time interaction term quantifying the effects of study condition on CTRA gene expression (based on change in the magnitude of parameter estimates and/or statistical significance of the Group × Time interaction).

4. Results

4.1. Descriptives

Table 1 presents sample characteristics for the overall sample and by condition at pre-test. Participants did not differ in pre-test demographic or biobehavioral characteristics (as indicated by nonsignificant Welch's *t*-tests; Table 1). Table 2 presents means and standard errors for loneliness by timepoint for the overall sample and by condition. As detailed in Martinez (2025), participants in the Extraversion condition reported significantly greater reductions in loneliness over time relative to controls.

4.2. Effects of extraverted behavior on CTRA

In primary analyses of the 53-gene CTRA composite, mixed effect linear models showed no significant group differences in CTRA change from pre- to post-intervention in either the primary (unconditional/unadjusted) analysis [$t(227) = 0.38$, $p = 0.705$] or the secondary covariate-adjusted analysis controlling for age, sex, race, BMI, smoking, alcohol consumption, illness symptoms, and 8 mRNA transcripts indicating prevalence of major leukocyte subsets within the circulating cell pool (CD4+ and CD8+ T lymphocytes, B lymphocytes, natural killer cells, and monocytes) [$t(207) = 0.97$, $p = 0.331$]. However, secondary analyses of CTRA gene regulation using a more complex genome-wide bioinformatic analysis of genes showed a significant Group × Time interaction consistent with an intervention-induced reduction in CTRA gene expression. Among 521 gene transcripts showing >1.5-fold differential change over time in the Extraversion condition v. Control group (i.e., > 1.5-fold Group × Time interaction; 115 genes relatively upregulated and 406 relatively downregulated), TELiS promoter-based bioinformatic analysis indicated a significant relative reduction in inflammatory NF-κB activity (0.67-fold, −0.57 log2 ratio ± SE 0.26, $p = 0.028$), a significant relative increase in antiviral IRF activity (1.23-fold, 0.30 ± 0.12, $p = 0.016$), and a significant relative decrease in sympathetic nervous system-related CREB activity (0.86-fold, −0.21 ± 0.07, $p = 0.005$; Fig. 2).

Table 1
Sample characteristics at pre-test: means, standard errors, and proportions for overall sample and by condition with welch's t-tests assessing condition differences.

Variable	Control	Extraversion	Overall Sample	*t*(*df*)	*p*
Age	21.80 (1.03)	21.21 (0.64)	21.51 (0.61)	0.48 (96.59)	0.632
BMI	24.37 (0.70)	24.06 (0.80)	24.22 (0.53)	0.29 (114.94)	0.773
Female	73 %	83 %	78 %	−1.28 (114.56)	0.202
Hispanic	42 %	51 %	46 %	−1.00 (116.89)	0.319
Asian	42 %	31 %	36 %	1.27 (116.69)	0.208
Black/African American	10 %	3 %	7 %	1.45 (97.21)	0.151
Smoke Regularly	2 %	0 %	1 %	1.00 (59.00)	0.321
Drink Regularly	2 %	0 %	1 %	1.00 (59.00)	0.321
Illness Symptoms	7 %	12 %	9 %	−0.97 (109.03)	0.333

Note. BMI = Body mass index. Smoke regularly = smoke tobacco products every day or almost every day. Drink regularly = 8 drinks or more per week for women; 15 drinks or more per week for men. Illness symptoms = illness symptoms within the past 2 days including cold, flu, or digestive issues.

Table 2
Loneliness: means and standard errors by timepoint for overall sample and by condition.

	Time 1 (Pre-Test)	Time 2 (Post-Test)	Time 3 (Follow-Up)
Control	2.52 (0.11)	2.52 (0.15)	2.41 (0.15)
Extraversion	2.38 (0.13)	2.06 (0.13)	2.33 (0.15)
Overall Sample	2.45 (0.09)	2.30 (0.10)	2.33 (0.11)

4.3. Role of loneliness

To determine whether reductions in loneliness might contribute to the intervention's effects on CTRA gene expression, we conducted additional secondary bioinformatic analyses that quantified Extraversion intervention effects on CTRA-related transcription factor activity after controlling for concomitant changes in loneliness. Results suggested that changes in loneliness partially account for the Extraversion intervention's Group × Time interaction effect on both immunoregulatory transcription factors, reducing group differences in NF-κB activity (0.95-fold, −0.07 ± 0.27, $p = 0.779$; Fig. 3) and IRF activity to

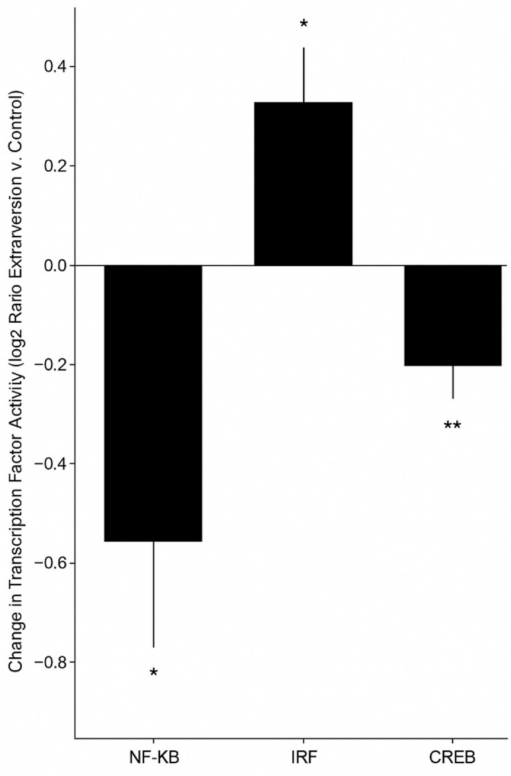

Fig. 2. Extraversion intervention effect on transcription factor activity. Data represent group differences (Extraversion – Control) in the magnitude of transcription factor activity change over time (Post-test – Pre-test) in genome-wide bioinformatic analyses of NF-kB pro-inflammatory signaling pathway, antiviral IRF signaling pathway, and adrenergic-responsive CREB signaling pathway. Values indicate the log2 ratio of transcription factor-binding motifs for each transcription factor in core promoter DNA sequences of genes showing 1.5-fold differential change from Week 0 to Week 8 in participants randomized to the Extraversion v. Control group (i.e., >1.5-fold Group × Time interaction).

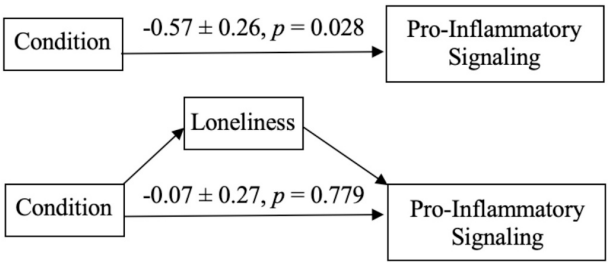

Fig. 3. Partial mediation of changes in loneliness between condition and pro-inflammatory signaling. Condition exerted a main effect on reduced pro-inflammatory signaling (top model), but this effect becomes nonsignificant when controlling for changes in loneliness (bottom model), suggesting changes in loneliness partially explain the intervention's effect on pro-inflammatory signaling.

nonsignificance (1.14-fold, 0.19 ± 0.11, $p = 0.085$; Fig. 4). However, the effect of the Extraversion intervention on CREB activity was not fully abrogated by controlling for decreases in loneliness, and a significant residual association remained (0.88-fold, -0.18 ± 0.08, $p = 0.017$). These patterns indicate that changes in loneliness may mediate a significant portion of the Extraversion intervention's effect on the immunological signaling components of the CTRA (i.e., NF-κB, IRF) but do not mediate intervention effects on the neural signaling component (i.e., CREB).

4.4. Persistence of CTRA effects

Analyses of change in CTRA gene expression from baseline to 1-month post-intervention showed no significant Group × Time interaction (i.e., did not indicate that CTRA intervention effects were maintained at 1-month follow-up). This was true for both the pre-specified CTRA composite score analyses [unconditional: $t(227) = -1.42$, $p = 0.157$; covariate-adjusted: $t(207) = -1.23$, $p = 0.218$] and the more complex secondary genome-wide bioinformatic analyses (NF-κB: 1.10-fold, 0.13 ± 0.19, $p = 0.492$; IRF: 1.00-fold, -0.01 ± 0.08, $p = 0.966$; CREB: 0.95-fold, -0.08 ± 0.04, $p = 0.083$).

5. Discussion

In the present randomized controlled intervention, participants who were randomized to act more sociable for 6 weeks showed significantly greater reductions in CTRA gene expression relative to controls. The intervention group also reported reduced subjective loneliness, and these loneliness reductions seemed to partially account for most of the intervention's effects on CTRA-characteristic inflammatory and anti-viral gene regulation. Collectively, these results suggest that intentionally increasing sociable behavior may be one effective strategy for reducing both loneliness and the adverse immunoregulatory correlates of loneliness involving elevated inflammatory gene expression and reduced innate antiviral response. However, there are two significant limitations on these effects. First, the duration of these effects was limited, and group differences in CTRA gene expression did not persist at 1-month follow-up after the intervention. Second, significant CTRA changes were observed only using a secondary analysis involving Group × Time interactions in genome-wide bioinformatic analyses of CTRA-related transcription control pathways. By contrast, our pre-registered analyses of a 53-gene CTRA composite score showed no significant effects. As such, the present results should be treated with caution until replicated in future research.

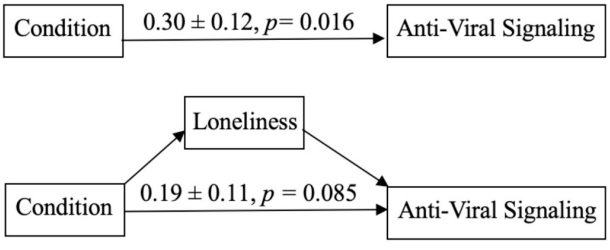

Fig. 4. Partial mediation of changes in loneliness between condition and anti-viral signaling. Condition exerted a main effect on greater anti-viral signaling (top model), but this effect becomes nonsignificant when controlling for changes in loneliness (bottom model), suggesting changes in loneliness partially explain the intervention's effect on anti-viral signaling.

The current findings are consistent with previous research showing that other social behavior interventions (e.g., performing acts of kindness; Nelson-Coffey et al., 2017; Regan et al., 2022) and stress-reduction protocols (e.g., mindfulness; Creswell et al., 2012) can also reduce CTRA gene expression profiles. Given the experimental nature of these studies, the present data add to a growing body of research suggesting that social behavior can exert causal effects on CTRA gene expression. These findings also advance previous correlational research that link social (dis)connection to CTRA gene expression and other aspects of immune function and health (e.g., Cole et al., 2015a; Cole et al., 2015b; Fredrickson et al., 2015), and they raise the possibility that intentionally increasing sociable behavior could be an effective strategy for protecting health against the adverse effects of perceived social isolation.

This research offers further insight into the mechanisms connecting sociality and physical health at the molecular level and raises additional questions about the durability of intervention effects. While previous studies suggest that CTRA effects are maintained at 1-week follow-up (Nelson-Coffey et al., 2017; Regan et al., 2022), the present study suggests intervention-facilitated enhancements to immune profile dissipate within 1 month following post-test. Additional research is needed to replicate these observations, and future studies could also examine CTRA expression with greater frequency following an intervention (e.g., every 1 or 2 weeks following post-test) to estimate the durability of CTRA effects with greater precision. Other research efforts could test how intervention-facilitated behavior change might be upkept following post-test to maintain immune-related benefits.

Lastly, this longitudinal, pre-registered experiment implicates reduced loneliness as a key mechanism connecting sociality to physical health. This experimental finding corresponds to other research implicating loneliness as a candidate mechanism of CTRA expression (Cole et al., 2015b; Creswell et al., 2012). The identification of loneliness as a link between social processes and CTRA gene regulation also maps well on the conceptual "CTRA signal transduction" pathway, which proposes that central nervous system (threat perception) processes offer the first link between the social environment and cellular signaling that, ultimately, impact CTRA gene regulation (Cole, 2019). Loneliness, after all, is primarily a cognitive (subjective) affliction that is defined more by *perceptions* of social isolation than by objectively measured social interaction (Hawkley & Cacioppo, 2010).

5.1. Limitations and future directions

The present study involved a pre-specified genomic profile hypothesis involving the CTRA and was not designed or powered for a comprehensive genome-wide exploratory analysis that might uncover additional genomic pathways or individual genes that might be regulated by sociable behavior. Discovery of other genomic correlates of extraverted behavior is an important topic for future research in larger samples. The present study also lacked any direct measures of immune cell function (e.g., cytotoxic activity, cytokine production) or disease resistance, and so the health significance of the present genomic effects remains to be determined in future research. Previous research has found the CTRA gene expression profile to predict health outcomes in humans (Antoni et al., 2016; Knight et al., 2019; Simons et al., 2017;

Taylor et al., 2023) and to mediate the effects of stress in experimental animal models of cardiovascular disease, cancer, and infectious disease (Cole et al., 2015a,b; Heidt et al., 2014; Powell et al., 2013; Sloan et al., 2010), but it is unclear what the health significance of the present CTRA effects would be in the context of the generally healthy community sample of young adults studied here. As such, future research will be required to quantify the health/disease impact of intentionally increasing extraverted behavior. Given that this is the first analysis relating experimentally induced extraverted behavior to CTRA gene expression, the present results need to be replicated in other samples and contexts. This is particularly important in light of the fact that our primary pre-specified multi-gene composite score measure of CTRA activity did not show a significant effect of the intervention. Although the pre-specified composite score approach to CTRA measurement is known to be less sensitive than the transcription factor bioinformatic analysis that yielded significant results in this study, it will be important to replicate these findings in additional samples to determine whether the nonsignificance of composite score analyses reflects a false negative finding (e.g., due to limited statistical power). Another limitation regards the relatively small effect sizes observed in this study; however, the present findings are comparable in magnitude to CTRA effects observed in other randomized controlled trials of behavioral interventions (e.g., Creswell et al., 2012; Dutcher et al., 2022). Taken together, such findings should be conservatively interpreted, and replication efforts will benefit from the effect size estimates and initial findings derived from this study.

Our findings should also be cautiously interpreted in terms of their generalizability given that our sample consists primarily of undergraduate students. Like other research in the behavioral sciences (Henrich et al, 2010), our current study involves a readily available college sample of young adults. A strength of our sample, however, includes its racial-ethnic diversity, with relatively high representation of Hispanic (46 %) and Asian (36 %) participants. Still, additional research among samples with greater diversity in other individual and demographic differences (e.g., age) is needed to replicate main effects and examine whether and how these effects might be moderated by these differences.

A final limitation is the relatively transient impact of this intervention, with experimental intervention effects reverting to nonsignificance by 1 month following the cessation of an extraverted behavior protocol. Accordingly, developing interventions that can produce more sustainable behavioral changes, and therefore, more enduring changes in immune regulation, will be important for addressing the health impacts of loneliness and social adversity. People may find that acting more sociable than usual, even when they are personally motivated to do so, can be challenging for an extended period of time. Mixed-methods research that examines participant experiences in an extraversion intervention suggests, on a preliminary basis, that instructing participants to make more specific, actionable plans in their efforts to be more sociable could be fruitful (Martinez et al., 2025). In addition, encouraging participants to be more caring and other-focused in their social interactions (as opposed to being more self-focused about the quality of their "social performance;" Martinez et al., 2025) might help them more enjoyably engage in more social interactions over time. Future interventions could also involve more frequent contact and support with participants during the immediate intervention period and during follow-up.

5.2. Conclusions

Intentionally increasing extraverted (sociable) behavior can reduce genomic measures of CTRA-related gene regulation involving pro-inflammatory signaling pathways (NF-kB), impaired innate antiviral responses (IRF) and neural signaling (CREB). These changes are associated with reductions in loneliness and raise the possibility that intentionally increasing extraverted behavior could be one potential strategy for addressing the health risks associated with loneliness.

CRediT authorship contribution statement

Ramona L. Martinez: Writing – original draft, Visualization, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Sonja Lyubomirsky:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition. **Steve W. Cole:** Writing – review & editing, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2026.106299.

Data availability

Data will be made available on request.

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