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Social connection and gene regulation during the COVID-19 pandemic: Divergent patterns for online and in-person interaction

Jeffrey G. Snodgrass, Shawna Bendeck, Katya Xinyi Zhao, Seth Sagstetter, Michael G. Lacy, Cody Nixon, Julia R. Branstrator, Jesusa M.G. Arevalo, Steven W. Cole

ARTICLE INFO

Keywords:
Social genomics
CTRA
Online social interaction
Loneliness
Eudaimonia

ABSTRACT

Background: Social connection has been linked to reduced disease risk and enhanced antiviral immunity, but it is unclear whether online social connections have similar effects to those previously documented for in-person/offline social relationships, or whether online connections can substitute for in-person social relations when the latter are restricted. We examined this question in the context of the COVID-19 pandemic, focusing specifically on an immune system gene regulation profile known as the conserved transcriptional response to adversity (CTRA), which is characterized by up-regulation of proinflammatory genes and down-regulation of genes linked to innate antiviral responses and antibody production.

Methods: We analyzed CTRA RNA profiles in blood samples from 142 healthy young adults (69% female, 87% white) during the “social distancing” period of the COVID-19 pandemic. Mixed effect linear models quantified the relation of CTRA gene expression to measures of in-person social connection (number of friends, social eudaimonia, loneliness) and online psychosocial connection (online loneliness, perceived social value in online leisure and educational contexts, and internet use) while controlling for demographic and health factors.

Results: Multiple indicators of in-person and generalized social connection were associated with lower CTRA gene expression, whereas no measure of online social connection showed any significant association with CTRA gene expression.

Conclusion: Experiences of in-person social connection are associated with reduced CTRA gene expression during a period of restricted social interaction. In contrast, online social relationships show no such association. Digitally mediated social relations do not appear to substantially offset the absence of in-person/offline social connection in the context of immune cell gene regulation.

1. Introduction

The negative health impacts of social isolation and felt loneliness are well-documented (Hawkley and Cacioppo, 2010). This includes how isolation and loneliness are associated with alterations in immune biology, of which increases in the stress-induced gene expression (RNA) profile known as the “conserved transcriptional response to adversity” (CTRA) are of particular interest here (Cacioppo et al., 2015a; Cole, 2009; Cole et al., 2015b; Creswell et al., 2012). The CTRA profile is induced in immune cells (leukocytes) by activation of flight-or-flight stress responses from the sympathetic nervous system (Heidt et al., 2014; McKim et al., 2018; Powell et al., 2013), and involves up-regulated expression of genes involved in inflammation and down-regulated expression of genes linked to innate antiviral responses (Cole, 2014, 2019). Research has also linked positive feelings of social support, connection, and resilience with reductions in the CTRA (Kohrt et al., 2016; Nelson-Coffey et al., 2017). This latter line of research also documents how experiencing life as socially meaningful and purposeful

☆ We acknowledge support from the National Science Foundation (#2042612), the National Institutes of Health (P30 AG017265), and the Foundation for Psychocultural Research.

* Corresponding author.

E-mail address: jeffrey.snodgrass@colostate.edu (J.G. Snodgrass).

https://doi.org/10.1016/j.psyneuen.2022.105885

Received 10 May 2022; Received in revised form 27 July 2022; Accepted 27 July 2022
Available online 29 July 2022
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altered expression of genes involved in inflammation and innate anti-
time within the scope of the COVID pandemic

Building on such prior research and thinking, we aimed to
illuminate a potentially important source of health resilience during this
expression during the pandemic. Identifying that association would

COVID-19 lockdowns, self-isolations, and quarantines reduce face-
to-face interaction, and can unintentionally harm social identities, re-
lationships, and experiences (Groarke et al., 2020; Hwang et al., 2020;
Kasar and Karaman, 2021; Killgore et al., 2020; Palgi et al., 2020; Van
Tilburg et al., 2021; Wickens et al., 2021), with rising prevalence of
isoion and loneliness potentially diminishing antiviral immunity
when it is direly needed (Cole et al., 2021; Dececahe et al., 2020;
Matts dos Santos, 2020). However, the current pandemic has also
increased the frequency and salience of online interactions for connec-
tion, meaning, and identity (Hajek and König, 2021; Shah et al., 2020;
Wiederhold, 2020a; Wong et al., 2021). Prior research among distinctive
subcultural groups (such as intensive video game players) has illumi-
nated how online interactions can promote health and well-being by
fostering meaningful virtual social identities and relationships (Carra-
x et al., 2018; Johannes et al., 2020; Jones et al., 2014; Karedfeh-Winther,
2014; Snodgrass et al., 2018a), including evidence specifically linking
such processes to reduced CTRA gene expression (Snodgrass et al., 2022,
2019, 2018b). Building on such prior research and thinking, we aimed to
identify in our study whether emerging adults’ (Arnett, 2000) strength
of online social connection might be associated with reduced CTRA
gene expression during the pandemic. Identifying that association would
illuminate a potentially important source of health resilience during this
crisis, as CTRA gene regulation would generally impair antiviral re-
sponses to SARS-CoV-2 while amplifying the inflammatory dynamics
that promote pulmonary inflammation and COVID-19 disease (Gelaye
et al., 2020).

Motivated by such prior theory and findings, we investigated within
a sample of U.S. undergraduate students (N = 144) how face-to-face and
online social experiences during the spring 2021 academic semester – a
time within the scope of the COVID pandemic – were associated with
altered expression of genes involved in inflammation and innate anti-
Viral activity (CTRA). Emerging adults such as members of this student
sample have high rates of self-reported loneliness (Hawkey and Cacioppo,
2010; Hopmeyer et al., 2022; Lim et al., 2019; Luhmann and
Hawkey, 2016; Matthews et al., 2019), with adults ages 18–22 being the
loneliest generation according to one recent report (Demarinis,
2020). Emerging adults also rely extensively on online social connec-
tions as a mode of ordinary interaction as well as to stave off loneliness
(Hood et al., 2018; Nowland et al., 2017; Reissmann et al., 2018;
Schiano et al., 2014; Turkle, 2012), including during the pandemic
(Towner et al., 2021), making this population highly relevant for our
study. Further, assessing CTRA within our sample was particularly
appropriate as an indicator of molecular well-being during the COVID
pandemic, given CTRA’s inverse component of gene transcripts involved
in Type I interferon antiviral responses (Cole, 2019) and its direct
pro-inflammatory component, both of which would tend to impair im-
mune responses to SARS-CoV-2 and promote lung inflammation and
COVID-19 disease (Gelaye et al., 2020).

To examine CTRA profiles in relation to social interaction among our
study participants, we used mixed effect linear models to analyze rela-
tionships between our in-person/offline and online psychosocial well-
being indicators and average expression across a pre-specified set of 45
CTRA indicator genes within each person’s circulating white blood cell
pool, while controlling for key demographic and health factors. Key
psychosocial predictors included self-reported loneliness and positive
experiences of social identity and connection, as reported in relation to
both offline and online contexts. We also used psychological anthropo-
logical interview methods involving free lists, pile sorts, and cultural
consensus analysis (Dengah et al., 2020) to develop contextually sensi-
tive scale measures of study participants’ congruence with attributes
that were culturally valued by members of this student population in
online leisure and educational settings. We considered these cultural
congruence measures – what anthropologists call “cultural consonance,”
which has been shown to be associated with health in a variety of cul-
tural contexts (Dressler, 2017) – as indicators of self-perceived personal
value within local society, which complemented our study’s more
standard psychosocial well-being measures such as self-reported lone-
liness and eudaimonia. (See Appendix A for more detail on this inter-
viewing and scale construction procedure).

2. Materials and methods

2.1. Participants and procedure

2.1.1. Recruitment

In December 2020, we placed psychosocial well-being, demographic,
and other measures of interest to our study in an online questionnaire,
which served as a recruitment tool for our subsequent spring 2021 se-
mester blood collection. We invited students from large classes that
fulfilled Colorado State University’s (CSU) general education re-
quirements (and thus drew a relatively representative population of
students from across the university) to respond to this questionnaire.
We used network recruitment of participants with procedures inspired by
respondent-driven sampling – a relatively new method reminiscent of
“snowball” sampling (Heckathorn and Cameron, 2017). Following this
approach, we obtained participants by distributing questionnaire in-
itations to a convenient group of “seeds,” who were then asked (with incentives) to forward the survey invitation to others in their personal
networks. This was done to increase our chances of obtaining a sample
to better represent the CSU undergraduate student population. We
received 197 responses to this initial phase of the questionnaire.
Beginning February 2021, we invited those December 2020 study par-
ticipants to respond to a second phase of the questionnaire, though this
time describing their current 2021 experiences. We continued with our
network recruitment methods, advising all questionnaire respondents
that we would also be inviting them to contribute blood samples for the
immune biology component of our study, with us providing each
blood-draw participant $25. All participants provided informed consent
prior to participation in each phase of study, including the blood-draw,
and all procedures were approved by the Institutional Review Board of
Colorado State University.

2.1.2. Blood collection and transcriptome profiling

We invited those who responded to the fall 2020 and spring 2021
version of the questionnaire to meet with us in our CSU campus lab for
the blood-draw. We collected samples using a commercially available
microfluidic blood collection system (Tasso-M20, 2020), which allows
participants to self-collect blood samples with little discomfort and
minimal contact with researchers, important during this phase of the
pandemic. The participant simply sterilized the blood draw field and
minimal contact with researchers, important during this phase of the
pandemic – what anthropologists call “social eudaimonia” (Keyes, 2009,
1998; Petrilio et al., 2015; Ryff and Singer, 2008) – can be reflected in reduced
CTRA (Cole et al., 2015b; Fredrickson et al., 2013, 2015; Kitayama et al.,
2016; Snodgrass et al., 2022, 2019). In the current study, we examine
whether experiences of loneliness and positive social connection and
meaning during the “social distancing” period of the COVID-19
pandemic were associated with altered CTRA gene expression, and
whether digital social connection, which theoretically might compen-
sate for deficits in in-person social contact, might be associated with
reduced CTRA.

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reduced CTRA.
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chemical desiccant pack to complete the drying process and prevent hydrolysis. Blood samples were collected in face-to-face meetings with respondents at our university research laboratory, refrigerated within 15 min, and subsequently frozen in daily batches at −30 °C for up to 3 months until being shipped to the UCLA Social Genomics Core Laboratory for gene expression analysis. Genome-wide transcriptional profiling was conducted using methods previously described (Cole et al., 2020; Snodgrass et al., 2018b) and validated as showing good correspondence to results from gold standard venipuncture blood samples for the bio-informatic quantities analyzed here (e.g., CTRA profile) (Kohrt et al., 2016; McDade et al., 2016). Briefly, RNA was mobilized out of two Tasso-M20 sample matrix cylinders by incubation in a standard RNA stabilization buffer (Qiagen RLT), extracted using standard methods (Qiagen RNAeasy), converted to cDNA using a high-efficiency mRNA-stabilization buffer (Qiagen RLT), and subject to multiplex sequencing on an Illumina NovaSeq instrument (Lexogen Services, GmbH), all following the manufacturer’s standard protocols for low-mass RNA samples. Sequencing targeted 5 million single-stranded reads per sample (achieved average = 8.6 million), each of which was mapped to the GRCh38 reference human transcriptome using the STAR aligner (Dobin et al., 2013) (average 93.5% mapping rate), with transcript abundance quantified as gene-specific reads per million total mapped reads. All samples passed endpoint quality control criteria and were retained for analysis. Gene expression values were log2-transformed to stabilize variance for linear statistical model analysis as described below.

2.2. Psychosocial experience and well-being measures

2.2.1. In-person and global experience

In-person/offline loneliness: We used a previously validated scale asking about how often our respondents felt over the past few weeks that they lacked companionship, felt left out of events, and felt isolated from others (Hughes et al., 2004), wording those items to explicitly ask about offline contexts in each case. Respondents rated the frequency of each of their experiences with each of these 3-point Likert items (1 = hardly ever, 2 = some of the time, 3 = often), and we assigned as their loneliness score the mean across items (Cronbach’s alpha = 0.80).

Generalized social eudaimonia (participants were not asked to distinguish between offline and online life): We used the five social items from the 14-item Mental Health Continuum-Short Form (MHC-SF), which asked respondents the extent that they felt over the past few weeks like they contributed to society, that they belonged to a community, that society was becoming a better place, that people were good, and that society made sense to them (Keyes, 2009; Lamers et al., 2011). This scale has been widely used in research on well-being in general, as well as its more specific relation to CTRA (e.g., Fredrickson et al., 2015, 2013). Respondents are asked to rate how frequently they experienced each item (1 = almost never, 2 = once or twice, 3 = approximately once per week, 4 = two or three times per week, 5 = almost every day, and 6 = every day). Assigned score was the mean across items (Cronbach’s alpha = 0.80).

College friends: We asked respondents to report approximately how many CSU undergraduate students they counted as close friends (i.e., people with whom they commonly sent and received text messages, which we learned was a good way to assess the importance of a friendship for members of a contemporary US undergraduate population, as students would only regularly send text messages throughout the day to their close friends), 0–2, 3–5, 6–10, 11–15, or more than 15.

2.2.2. Online experience

Online loneliness: We used the same scale as described previously but here asked specifically in relation to online contexts how often respondents felt over the past few weeks that they lacked companionship, felt left out of events, and felt isolated from others (Hughes et al., 2004). As before, items had a 3-point response format (1 = hardly ever, 2 = some of the time, 3 = often), and the scale score was the mean across items (Cronbach’s alpha = 0.72).

Cultural consonance online leisure (congruence with traits culturally valued in online social leisure contexts): We asked respondents to think about how they saw themselves in online social leisure contexts that were important to them over the past few weeks. We prompted them that this could be, for example, an online group or community where they relaxed and had fun, including social media platforms, gaming groups, or community discussion boards such as Reddit. The important thing, we said, was that the online social context felt meaningful to them. Then, we asked them to report how closely each of a list of 12 traits culturally valued in those online contexts described them: creative and interesting; friendly and inclusive; fun and funny; open-minded; perceptive; detached and anonymous (reverse coded); flexible and easygoing; socially connected to others; a good communicator; knowledgeable and capable; engaged and interactive; respected. Respondents rated those traits according to how closely each attribute described them: 1 = very slightly or almost not at all, 2 = a little bit, 3 = moderately, 4 = to a great extent, with the scale score again being the mean across items (Cronbach’s alpha = 0.89). (See Appendix A for detail on the psychological anthropological interviewing methods we used to develop this scale measure.)

Cultural consonance online educational (congruence with traits culturally valued in online educational settings): We asked respondents to think about how they saw themselves over the past few weeks in online educational contexts like Zoom and/or Microsoft Teams meetings where they had classes or in online educational class discussion boards and groups. They reported how closely each of a second list of 12 culturally valued traits described them: a good communicator; knowledgeable and capable; detached and anonymous (reverse coded); hardworking and productive; flexible and easygoing; open-minded; constructive; professional and well put together; perceptive; prepared; engaged and interactive; friendly and inclusive. As with the other cultural consonance scale, respondents again rated how closely each of the following described them: 1 = very slightly or almost not at all, 2 = a little bit, 3 = moderately, 4 = to a great extent. Scale scores are means across items (Cronbach’s alpha = 0.87) (See Appendix A for more detail on this measure.).

Internet activity: Respondents reported their amount of internet activity over the past few weeks, estimating how many hours (0–1, 1–2, 2–3, 3–4, 4–5, 5–6, More than 6) they daily engaged in each of the following five activities: Streaming entertainment (e.g., Netflix, YouTube, TikTok, Spotify, etc.); Social media (Instagram, Tumblr, Twitter, Facebook, etc.); Gaming (including single player and multiplayer modes); Voice or video conversations with friends and/or family (via phone, FaceTime, Discord, Skype, Zoom, etc., as this measure included standard landline phone activity and also communication via mobile cellular networks and the internet); School or work-related activities (Zoom, Microsoft Teams, Blackboard/ Canvas, etc.).

2.3. Demographic, health, and behavioral measures

Standard covariates used in our regression analysis were collected from participants either from the online questionnaire or during the blood-draw meeting, including age, gender (0 = female, 1 = male, 2 = non-binary), and ethnicity (0 = non-white, 1 = white). BMI was calculated from self-reported height and weight. Respondents also reported their exercise level: 0 = very little to none (only very occasional or virtually no exercise), 1 = low (perhaps you visit a gym, run, etc. once a week or so, but not too extensive or very regular), 2 = moderate (regular exercise, e.g., at least 2–3 times/week, at least somewhat vigorous), 3 = high (vigorous exercise at least 3–4 times/week), 4 = professional athlete-level fitness (training for competitive road races, etc.). They reported whether they smoked (0 = never, 1 = at least sometimes), if they consumed alcohol on a typical weekday (0 = no, 1 = yes), and about average weekend alcohol consumption (0 = none, 1 =
=1–5 drinks, 2 =6 or more drinks).

2.4. CTRA indicator genes

The primary outcome analyzed in this study was a contrast computed over a pre-specified set of 53 CTRA indicator genes used in previous research (Cole et al., 2020; Fredrickson et al., 2015, 2013), including 19 pro-inflammatory genes (IL1A, IL1B, IL6, IL8, TNF, PTGS1, PTGS2, FOS, FOSB, FOSL1, FOSL2, JUN, JUNB, JUND, NFKB1, NFKB2, REL, RELA, RELB) that serve as positive indicators of the CTRA profile, and 34 genes involved in Type I interferon responses (GBP1, IFI16, IFI27, IFI27L1–2, IFI30, IFI35, IFI44, IFI44L1, IFI6, IFI11, IFIT1–3, IFIT5, IFITM1–3, IFITM4P, IFITM5, IFN1B1, IRF2, IRF7–8, MX1–2, OAS1–3, OASL) and antibody synthesis (JCHAIN, IGLL1, IGLL3P), which were reverse-scored to reflect their role as inverse indicators of the CTRA profile (Cole et al., 2020; Fredrickson et al., 2015, 2013). Among this set of 53 indicator genes, 8 transcripts showed minimal levels of expression (predominately 0 values; FOSL1, IFITM4P, IFITM5, IFNB1, IGLL1, IGLL3P, IL1A, IL6) and minimal variability (SD <0.5 log2 units) and were thus excluded from analysis to facilitate convergence of maximum likelihood statistical model estimation as described below.

2.5. Statistical analysis

Results are from mixed effect linear model analyses relating average expression of 45 z-score transformed CTRA indicator gene transcripts (with antiviral genes sign-inverted to reflect their inverse contribution to the CTRA profile, all treated as repeated measures) to key social predictors (again, z-scored) while controlling for age, gender, ethnicity, body mass index (BMI), exercise, smoking, and drinking (both weekday and weekend). Analyses were conducted using SAS PROC MIXED as previously described (Cole et al., 2020; Fredrickson et al., 2015), with maximum likelihood estimation of fixed effects for indicator gene (repeated measure within subjects), covariates (age, gender, ethnicity, BMI, exercise, smoking, drinking), and social measures as described above, with a fully saturated (unstructured) random effect variance-covariance matrix to accommodate heteroscedasticity across genes and heterogeneous correlations among residuals across genes. We first report relationships between CTRA indicator gene expression and our offline and generalized well-being measures: In-person/offline loneliness, Generalized social eudaimonia, and College friends. This is followed by analysis of relationships between CTRA and the key measures of online well-being: Online loneliness, Cultural consonance online leisure, Cultural consonance online educational, and Internet use (with separate analyses for each form of internet use).

3. Results

3.1. Sample characteristics

Table 1 presents descriptive statistics for study participants. The study sample was predominately female (69%), an average 20 years of age (SD 3 years), and 87 % White, with generally healthy BMI (mean 23.4 kg/m^2, SD 4.37). The mean for offline loneliness was just below 2 on the 3-pt response scale, i.e., a little less often than “some of the time.” Likewise, participants had a mean social eudaimonia score just above the midpoint of the 6-pt scale, slightly more than “approximately once per week.” The most common response for number of college friends was “3–5,” with 43.7 % of the sample reporting that category. Respondents reported slightly less online compared to offline loneliness, with a mean at between “hardly ever” and “some of the time.” On both cultural consonance scales, respondents reported having each of those

| Table 1 Sample Characteristics (n = 142 for all variables). |
|---------------------------------|----------------|----------------|
| Demographic, social experience, and health indicators | Mean (SD) or % | Cronbach's alpha |
| Gender | Female 69.0 % | | |
| Male 31.0 % | | |
| Age (years) | 20.2 (3.02) | | |
| White/Anglo ethnicity | 87.3 % | | |
| Non-Binary 12.7 % | | |
| Body Mass Index | 23.4 (4.37) | | |
| In-person/offline loneliness (1–3 scale) | 1.88 (0.62) | 0.80 |
| Generalized social eudaimonia (1–6 scale) | 3.36 (1.11) | 0.80 |
| College friends | “0–2” 28.2 % | | |
| “3–5” 43.7 % | | |
| “6–10” 28.5 % | | |
| “11–15” 26.8 % | | |
| Online loneliness (1–3 scale) | 1.69 (0.58) | 0.72 |
| Cultural consonance online leisure (1–4 scale) | 3.03 (0.57) | 0.89 |
| Cultural consonance online educational (1–4 scale) | 2.96 (0.53) | 0.87 |
| Exercise, times/week | “none” 12.0 % | | |
| “1” 35.2 % | | |
| “2–3” 34.5 % | | |
| “4–6” 16.2 % | | |
| “more than 4” 2.1 % | | |
| Smoker (at least occasionally vs. never) | 16.2 % | | |
| Drinks typically on weekdays (vs. not) | 19.0 % | | |
| Number of drinks on typical weekend | “0” 46.3 % | | |
| “1–5” 43.7 % | | |
| “6 or more” 9.9 % | | |
| Internet activity (hr./day) | “0–1” | “1–2” | “2–3” | “3–4” | “4–5” | “5–6” | “> 6” |
| Streaming entertainment | 5.6 % | 21.1 % | 29.6 % | 21.1 % | 9.2 % | 4.2 % | 9.2 % |
| Social media | 14.8 % | 35.2 % | 20.4 % | 16.2 % | 4.9 % | 4.2 % | 4.2 % |
| Gaming | 69.7 % | 14.8 % | 11.3 % | 2.1 % | 1.4 % | 0.0 % | 0.7 % |
| Voice/video conversations | 44.4 % | 39.4 % | 9.2 % | 4.2 % | 0.7 % | 0.0 % | 2.1 % |
| School or work activity | 2.1 % | 11.2 % | 17.6 % | 28.2 % | 11.3 % | 14.3 % | 15.5 % |
12 valued traits at roughly 3 on the 4-pt scale, or “moderately.” A typical study participant reported most frequently using the internet for online school or work activity (which presumably reflects the online-intensive nature of university education during the pandemic), with somewhat less time engaged in streaming entertainment and social media, and even fewer hours in gaming and voice or video conversations. Likewise, most respondents reported either low or moderate exercise (roughly a third of the sample for each category) and were non-smokers, who typically did not drink on the weekdays but with slightly over half of the sample drinking on the weekends.

Table 2 presents a correlation matrix for the in-person and online experience measures. Patterns of association were as expected, e.g., negative correlations between Offline loneliness and both Generalized social eudaimonia and College friends, positive correlations between Generalized (offline/online) social eudaimonia and congruence (consonance) with traits culturally valued in both online educational and online leisure settings, with the latter two measures also positively correlated with each other.

### 3.2. CTRA gene expression

#### 3.2.1. In-person/offline and global experience

Table 3 reports results quantifying the relation of CTRA gene expression (average expression of 45 CTRA indicator gene transcripts, with antiviral transcripts inversely scored) to multiple measures of in-person social connection, with all results adjusted for potentially confounding effects of age, gender, ethnicity, BMI, exercise, smoking, and drinking. As summarized in Fig. 1 (left), CTRA gene expression showed a significant positive association with offline loneliness (+0.028 mRNA abundance per SD loneliness ± 0.012 SE, p = .029) and a particularly strong negative association with generalized social eudaimonia (-0.044 ± 0.013, p < .001). CTRA gene expression also showed significant negative association with the number of college friends (-0.034 ± 0.013 RNA per SD, p = .009, corresponding to -0.042 ± 0.016 RNA per friend count category, p = .009). When all 3 measures of offline social experience were included in the same model, only general social eudaimonia emerged as a distinctly significant predictor (-0.032 ± 0.014, p = .026).

#### 3.2.2. Online experience

In parallel analyses of online social connection (Table 3 and Fig. 1, right), CTRA gene expression showed no significant association with online loneliness (+0.007 ± 0.012, p = .553). Nor did we identify significant associations between CTRA gene expression and cultural consonance online loneliness (+0.013 ± 0.012, p = 0.284) or cultural consonance online educational (-0.003 ± 0.012, p = 0.798). CTRA was also not significantly associated with amount of time spent online engaging with streaming entertainment (+0.013 ± 0.013, p = 0.315), social media (-0.007 ± 0.013, p = 0.624), gaming (+0.003 ± 0.013, p = 0.827), voice or video conversation (+0.023 ± 0.012, p = 0.065), or school or work activity (+0.000 ± 0.012, p = 0.976). Similarly, analyses

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### Table 2

#### Correlations among Key Predictors. (n = 142 for all variables).

| Variable                          | In-person/offline loneliness | Genlz. social eudaimonia | College friends | Online loneliness | Cultural consonance online educational | Cultural consonance online leisure | Streaming entertainment | Social media | Gaming | Voice/ Vid. conversations | School/ work activities |
|-----------------------------------|------------------------------|---------------------------|-----------------|-------------------|----------------------------------------|----------------------------------|--------------------------|-------------|--------|---------------------------|------------------------|
| In-person/offline loneliness      |                             |                           |                 |                   |                                        |                                  |                          |             |        |                          |                        |
| Genlz social eudaimonia           | -0.390***                    |                           |                 |                   |                                        |                                  |                          |             |        |                          |                        |
| College friends                   | -0.182                       | 0.341***                  | -0.002          |                   |                                        |                                  |                          |             |        |                          |                        |
| Online loneliness                 | 0.236**                      | -0.253**                  | -0.062          |                   |                                        |                                  |                          |             |        |                          |                        |
| Cultural consonance online leisure| -0.284***                    | 0.304***                  | 0.112           | -0.164            |                                        |                                  |                          |             |        |                          |                        |
| Cultural consonance online educational | -0.280***                  | 0.165*                    | -0.041          | -0.140            | 0.469***                                |                                  |                          |             |        |                          |                        |
| Streaming entertainment           | 0.265**                      | -0.170*                   | 0.015           | 0.040             | -0.094                                 | -0.093                           |                          |             |        |                          |                        |
| Social media                      | 0.058                        | -0.135                    | 0.014           | -0.003            | 0.051                                  | 0.076                            | 0.243**                  |             |        |                          |                        |
| Gaming                            | 0.035                        | -0.009                    | -0.028          | 0.017             | 0.084                                  | -0.046                           | 0.148                    | 0.023        |        |                          |                        |
| Voice/ Vid. conversations         | 0.030                        | 0.018                     | -0.089          | -0.052            | 0.135                                  | 0.098                            | 0.306***                 | 0.306        | 0.162  |                          |                        |
| School/work activities            | -0.056                       | -0.012                    | -0.146          | -0.035            | 0.174*                                 | 0.257**                          | 0.105                    | 0.042        | -0.095 | 0.298***                   |                        |

* p < .05
** p < .01
*** p < .001

### Table 3

#### Relationship between social experience and CTRA gene expression. (n = 142 for all variables).

| Social experience variable | Estimate | SE  | p-value |
|----------------------------|----------|-----|---------|
| Offline/ generalized       |          |     |         |
| In-person/offline loneliness| 0.028    | 0.012| 0.029   |
| Social eudaimonia          | -0.044   | 0.013| < 0.001 |
| College friends            | -0.034   | 0.013| 0.009   |
| Online loneliness          | 0.007    | 0.012| 0.553   |
| Consonance: Online leisure | 0.013    | 0.012| 0.284   |
| Consonance: Online educational | -0.003 | 0.012| 0.798   |
| Hours online               |          |     |         |
| Streaming entertainment    | 0.013    | 0.013| 0.315   |
| Social media               | -0.007   | 0.013| 0.624   |
| Gaming                     | 0.003    | 0.013| 0.827   |
| Voice/ video conversation  | 0.023    | 0.012| 0.065   |
| School/ work activities    | 0.000    | 0.012| 0.976   |

* Linear model regression parameter relating social experience predictors to log2 CTRA RNA abundance. All predictors are standardized.
including all measures of online social connection simultaneously also showed no significant CTRA association for any of those parameters (all \( p > .25 \)).

4. Discussion

In this study assessing social connection during the coronavirus social distancing era, multiple dimensions of offline and generalized social connection were associated with reduced CTRA gene expression in a sample of college undergraduates, whereas no dimension of online social connection showed any significant association with CTRA gene expression. These findings are consistent with a substantial body of previous literature pointing to important relationships between immune system gene regulation and both measures of social deprivation (loneliness) as well as positive social connections (such as social eudaimonia) (Cacioppo et al., 2015a; Cole et al., 2015b; Fredrickson et al., 2015; Kohrt et al., 2016; Snodgrass et al., 2019b). These findings point to how in-person social connections might serve as a source of health and disease resilience during crises such as the current pandemic (Cole et al., 2021; Dezecache et al., 2020; Mattos dos Santos, 2020), particularly given the key roles of innate antiviral responses and pro-inflammatory gene regulation in the pathogenesis of COVID-19 disease (Gelaye et al., 2020).

However, in seeking to extend such analyses to digital socialization, we did not find any support for the idea that stronger online social ties would be associated with improved antiviral immune biology, in ways that might potentially offset the reduced face-to-face social relations stemming from pandemic conditions. Prior research has pointed to how online interactions can foster meaningful virtual identities and relationships (Carras et al., 2018; Johannes et al., 2020; Jones et al., 2014; Kardefelt-Winther, 2014; Snodgrass et al., 2018a), and potentially alter immune biology and reduce the CTRA (Snodgrass et al., 2022, 2019b,a, 2018b). Nevertheless, our results do not support the idea that these online connections can substitute for in-person social relations as a major source of health resilience during the pandemic among this healthy sample of community-dwelling young adults, despite the risks of antiviral immunity being compromised due to rising rates of social isolation and felt loneliness (Cole et al., 2021; Dezecache et al., 2020; Mattos dos Santos, 2020). Online social interactions alone, then, do not appear here to reduce CTRA gene expression in the same way that has previously been implicated for in-person / offline social ties (Cacioppo et al., 2015a,b; Cole et al., 2015a, 2007), even when measured in parallel, as in this study. Further, online activities related to social media and gaming have been associated with increased stress, threat, and negative health outcomes (e.g., see Petry et al., 2014; Twenge et al., 2020), which might counter-balance any potential immune biology benefits to be had from increased digital connection. To these ideas, we would add that future research might profitably examine how emerging adults maintain their social lives across various in-person and online modes of connection combined, as distinctions between life offline and online can be artificial for this population (Bolander and Locher, 2020; Hirzalla and Zoonen, 2011; Slater, 2002).

This study is subject to several limitations, including a correlational study design, which precludes drawing definitive causal conclusions about how in-person and online social connection can serve as sources of health resilience. We controlled for demographic and biobehavioral factors that are potentially relevant to CTRA gene expression, i.e., age, gender, ethnicity, BMI, exercise, smoking, drinking. However, other unmeasured factors might be associated with both social experience and CTRA and thus confound the effects observed here. Use of a within-subject design involving longitudinal measurement of social parameters and CTRA may help clarify causal relations. Other limits include use of a convenience sampling strategy in college students (rendering uncertain the generalizability of the present findings to the population in general or to other subcultures) and absence of long-term follow-up on disease outcomes (so the health significance of the present gene expression effects remains to be defined in future research).

Despite these limitations, this study adds to an existing literature linking social connection and experience to measures of molecular well-being, by underscoring the key role played by offline and global (offline/online) social experience. However, these results suggest that online social interaction by itself is not likely to significantly offset, much less remediate, the adverse immunoregulatory impacts of diminished social contact in the face-to-face world. Given the health risks associated with CTRA activity (e.g., in the context of inflammation-related chronic diseases and viral infections) (Cole, 2019), these results underscore the need to understand more fully the psychological, neural, and immunologic pathways through which social connections influence physical health, and explore more fully the contexts and modalities in which digital interactions might be employed to help enhance the health-protective effects of offline or generalized social connections. To the extent that similar dynamics pertain in therapeutic interactions (which were not studied here), current modes of “teletherapy” (Bierbooms et al., 2020; Wiendold, 2020b) may also lack some secondary health benefits characteristic of face-to-face clinical encounters. This potential remains to be directly examined in future research, but it further underscores the importance of understanding the psychophysiology of human social interaction and its role in regulating immune function, health, and well-being.

Compliance with Ethical Standards

The research described in this article, including the use of appropriate informed consent procedures, has been reviewed and approved by the Colorado State University Institutional Review Board (IRB) for the protection of human subjects. The submitted work is original, and not under consideration elsewhere for publication.

Funding

We acknowledge financial support from the National Science Foundation (#2042612), the National Institutes of Health (P30 AG017265),
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