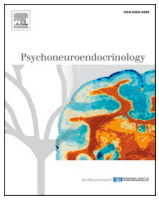
Psychoneuroendocrinology 144 (2022) 105885

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen



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

Jeffrey G. Snodgrass [a,*], Shawna Bendeck [b], Katya Xinyi Zhao [a], Seth Sagstetter [a], Michael G. Lacy [b], Cody Nixon [a], Julia R. Branstrator [c], Jesusa M.G. Arevalo [d], Steven W. Cole [d,e]

[a] Department of Anthropology and Geography, Colorado State University, Fort Collins, CO 80523-1787, USA
[b] Department of Sociology, Colorado State University, Fort Collins, CO 80523-1784, USA
[c] Department of Human Dimensions of Natural Resources, Colorado State University, Fort Collins, CO 80523, USA
[d] Division of Hematology-Oncology, Department of Medicine, University of California, Los Angeles School of Medicine, Los Angeles, CA 90095, USA
[e] Department of Psychiatry & Biobehavioral Sciences, University of California, Los Angeles School of Medicine, Los Angeles, CA 90095, USA

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 fight-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

– what has been referred to as *social eudaimonia* (Keyes, 2009, 1998; Petrillo 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 compensate for deficits in in-person social contact, might be associated with reduced CTRA.

COVID-19 lockdowns, self-isolations, and quarantines reduce face-to-face interaction, and can unintentionally harm social identities, relationships, 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 isolation and loneliness potentially diminishing antiviral immunity when it is direly needed (Cole et al., 2021; Dezecache et al., 2020; Mattos dos Santos, 2020). However, the current pandemic has also increased the frequency and salience of *online* interactions for connection, 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 illuminated how online interactions can promote health and well-being by fostering meaningful virtual social identities and relationships (Carras et al., 2018; Johannes et al., 2020; Jones et al., 2014; Kardefelt-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 responses 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 antiviral activity (CTRA). Emerging adults such as members of this student sample have high rates of self-reported loneliness (Hawkley and Cacioppo, 2010; Hopmeyer et al., 2022; Lim et al., 2019; Luhmann and Hawkley, 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 connections 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 immune 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 relationships 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 anthropological interview methods involving free lists, pile sorts, and cultural consensus analysis (Dengah et al., 2020) to develop contextually sensitive 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 cultural 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 loneliness and eudaimonia. (See Appendix A for more detail on this interviewing 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 semester blood collection. We invited students from large classes that fulfilled Colorado State University's (CSU) general education requirements (and thus draw 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 invitations 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 participants 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 affixed the Tasso-M20 to the skin over their deltoid muscle, just below their shoulder. Participants then pressed the Tasso-M20′s actuation button, which deployed a ring of microneedles to access blood and formed a weak vacuum to draw blood out of the capillaries and into a sample collection vessel at the bottom of the Tasso-M20 device. Members of our research team were available to offer support in the use of these devices. During February and March 2021, we collected blood from 144 individuals over a period of a month.

The Tasso-M20 devices delivered 4 samples of 17.5 μL ± 5 % (70 μL total) of whole blood into small cylindrical matrices in which plasma evaporated to preserve dried blood cells and plasma proteins. The dried blood was stored in an airtight foil bag at room temperature with a

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 bioinformatic 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 RNeasy), converted to cDNA using a high-efficiency mRNA--targeted enzyme system (Lexogen QuantSeq 3′ FWD), 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 intensive nor 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, IFI44L, IFI6, IFIH1, IFIT1–3, IFIT5, IFIT1L, IFITM1–3, IFITM4P, IFITM5, IFNB1, 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 28.2 % Non-Binary 2.8 %					
Age (years)		20.2 (3.02)					
White/Anglo ethnicity		87.3 %					
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" 25.4 % "11–15" 2.8 %					
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 % "3–4" 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" 46.5 % "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 (+.028 mRNA abundance per SD loneliness ± .012 SE, p = .029) and a particularly strong *negative* association with generalized social eudaimonia (−.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).

Table 3
Relationship between social experience and CTRA gene expression. (n = 142 for all variables).

Social experience variable	Estimate[a]	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			
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

[a] Linear model regression parameter relating social experience predictors to log2 CTRA RNA abundance. All predictors are standardized.

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 (+.007 ± 0.012, p = 0.553). Nor did we identify significant associations between CTRA gene expression and cultural consonance online leisure (+.013 ± .012, p = 0.284) or cultural consonance online educational (−.003 ± 0.012, p = 0.798). CTRA was also not significantly associated with amount of time spent online engaging with streaming entertainment (+.013 ± 0.013, p = 0.315), social media (−.007 ± 0.013, p = .624), gaming (+.003 ± 0.013, p = 0.827), voice or video conversation (+.023 ± .012, p = 0.065), or school or work activity (+.000 ± .012, p = 0.976). Similarly, analyses

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 leisure	Cultural consonance online educational	Streaming entertainment	Social media	Gaming	Voice/ Vid. conversations	School/ work
In-person/ offline loneliness	–										
Genlz social eudaimonia	-0.390***	–									
College friends	-0.182*	0.341***	–								
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	-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

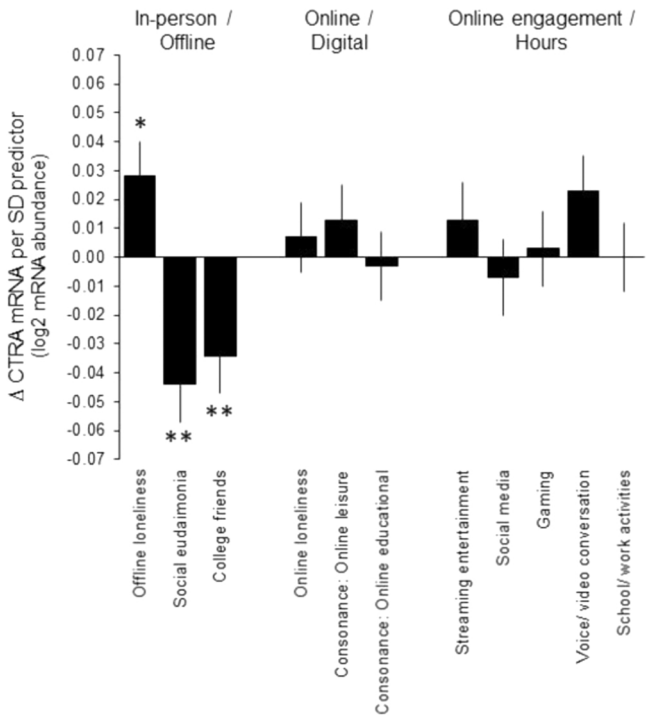


Fig. 1. Relationship between social experience and CTRA gene expression. (n = 142 for all variables).

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; Wiederhold, 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),

the Foundation for Psychocultural Research (https://thefpr.org/), and Colorado State University's (CSU) Department of Anthropology and Geography.

CRediT authorship contribution statement

J.G.S., M.G.L., and S.W.C designed research; J.G.S., S.B., K.X.Z., S.S., M.G.L., C.N., J.B., J.M.G.A., and S.W.C. performed research; J.G.S., S.B., K.X.Z., S.S., M.G.L., and S.W.C. contributed new reagents/analytic tools; J.G.S., S.B., K.X.Z., S.S., M.G.L., J.B., and S.W.C. analyzed data; and J.G.S., M.G.L., and S.W.C wrote the paper.

Declaration of Competing Interest

none.

Acknowledgments

We thank the CSU students who participated in our study's various phases and those who helped us with study participant recruitment and interviews.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2022.105885.

References

Arnett, J.J., 2000. Emerging adulthood: A theory of development from the late teens through the twenties. Am. Psychol. 55, 469–480.

Bierbooms, J.J.P.A., Haaren, M., van, IJsselsteijn, W.A., Kort, Y.A.W., de, Feijt, M., Bongers, I.M.B., 2020. Integration of online treatment into the "new normal" in mental health care in post–COVID-19 times: exploratory qualitative study. JMIR Form. Res. 4, e21344 https://doi.org/10.2196/21344.

Bolander, B., Locher, M.A., 2020. Beyond the online offline distinction: entry points to digital discourse. Discourse Context Media 35, 100383.

Cacioppo, J.T., Cacioppo, S., Capitanio, J.P., Cole, S.W., 2015a. The neuroendocrinology of social isolation. Annu. Rev. Psychol. 66, 733–767.

Cacioppo, J.T., Cacioppo, S., Cole, S.W., Capitanio, J.P., Goossens, L., Boomsma, D.I., 2015b. Loneliness across phylogeny and a call for comparative studies and animal models. Perspect. Psychol. Sci. 10, 202–212. https://doi.org/10.1177/1745691614564876.

Carras, M.C., Kalbarczyk, A., Wells, K., Banks, J., Kowert, R., Gillespie, C., Latkin, C., 2018. Connection, meaning, and distraction: a qualitative study of video game play and mental health recovery in veterans treated for mental and/or behavioral health problems. Soc. Sci. Med. 216, 124–132.

Cole, S.W., 2009. Social regulation of human gene expression. Curr. Dir. Psychol. Sci. 18, 132–137.

Cole, S.W., 2014. Human social genomics. PLOS Genet. 10, e1004601.

Cole, S.W., 2019. The conserved transcriptional response to adversity. Curr. Opin. Behav. Sci. 28, 31–37.

Cole, S.W., Hawkley, L.C., Arevalo, J.M., Sung, C.Y., Rose, R.M., Cacioppo, J.T., 2007. Social regulation of gene expression in human leukocytes. Genome Biol. 8, R189.

Cole, S.W., Capitanio, J.P., Chun, K., Arevalo, J.M., Ma, J., Cacioppo, J.T., 2015a. Myeloid differentiation architecture of leukocyte transcriptome dynamics in perceived social isolation. Proc. Natl. Acad. Sci. USA 112, 15142–15147.

Cole, S.W., Levine, M.E., Arevalo, J.M., Ma, J., Weir, D.R., Crimmins, E.M., 2015b. Loneliness, eudaimonia, and the human conserved transcriptional response to adversity. Psychoneuroendocrinology 62, 11–17.

Cole, S.W., Shanahan, M.J., Gaydosh, L., Harris, K.M., 2020. Population-based RNA profiling in add health finds social disparities in inflammatory and antiviral gene regulation to emerge by young adulthood. Proc. Natl. Acad. Sci. USA 117, 4601–4608. https://doi.org/10.1073/pnas.1821367117.

Cole, S.W., Cacioppo, J.T., Cacioppo, S., Bone, K., Del Rosso, L.A., Spinner, A., Arevalo, J. M.G., Dizon, T.P., Capitanio, J.P., 2021. The Type I interferon antiviral gene program is impaired by lockdown and preserved by caregiving. Proc. Natl. Acad. Sci. USA 118, e2105803118. https://doi.org/10.1073/pnas.2105803118.

Creswell, J.D., Irwin, M.R., Burklund, L.J., Lieberman, M.D., Arevalo, J.M.G., Ma, J., Breen, E.C., Cole, S.W., 2012. Mindfulness-based stress reduction training reduces loneliness and pro-inflammatory gene expression in older adults: a small randomized controlled trial. Brain, Behav. Immun. 26, 1095–1101. https://doi.org/10.1016/j.bbi.2012.07.006.

Demarinis, S., 2020. Loneliness at epidemic levels in America. Explore 16, 278–279. https://doi.org/10.1016/j.explore.2020.06.008.

Dengah II, H.J.F., Snodgrass, J.G., Polzer, E.R., Nixon, C., 2020. Systematic Methods for Analyzing Culture: A Practical Guide. Routledge.

Dezecache, G., Frith, C.D., Deroy, O., 2020. Pandemics and the great evolutionary mismatch. Curr. Biol. 30, R417–R419. https://doi.org/10.1016/j.cub.2020.04.010.

Dobin, A., Davis, C.A., Schlesinger, F., Drenkow, J., Zaleski, C., Jha, S., Batut, P., Chaisson, M., Gingeras, T.R., 2013. STAR: ultrafast universal RNA-seq aligner. Bioinformatics 29, 15–21. https://doi.org/10.1093/bioinformatics/bts635.

Dressler, W.W., 2017. Culture and the Individual: Theory and Method of Cultural Consonance. Routledge.

Fredrickson, B.L., Grewen, K.M., Coffey, K.A., Algoe, S.B., Firestine, A.M., Arevalo, J.M. G., Ma, J., Cole, S.W., 2013. A functional genomic perspective on human well-being. Proc. Natl. Acad. Sci. USA 110, 13684–13689. https://doi.org/10.1073/pnas.1305419110.

Fredrickson, B.L., Grewen, K.M., Algoe, S.B., Firestine, A.M., Arevalo, J.M., Ma, J., Cole, S.W., 2015. Psychological well-being and the human conserved transcriptional response to adversity. PLOS One 10, e0121839.

Gelaye, B., Foster, S., Bhasin, M., Tawakol, A., Fricchione, G., 2020. SARS-CoV-2 morbidity and mortality in racial/ethnic minority populations: a window into the stress related inflammatory basis of health disparities. Brain Behav. Immun. Health 9, 100158. https://doi.org/10.1016/j.bbih.2020.100158.

Groarke, J.M., Berry, E., Graham-Wisener, L., McKenna-Plumley, P.E., McGlinchey, E., Armour, C., 2020. Loneliness in the UK during the COVID-19 pandemic: cross-sectional results from the COVID-19 Psychological Wellbeing Study. PLOS One 15, e0239698.

Hajek, A., König, H.-H., 2021. Social isolation and loneliness of older adults in times of the COVID-19 pandemic: can use of online social media sites and video chats assist in mitigating social isolation and loneliness. GER 67, 121–124. https://doi.org/10.1159/000512793.

Hawkley, L.C., Cacioppo, J.T., 2010. Loneliness matters: a theoretical and empirical review of consequences and mechanisms. Ann. Behav. Med. 40, 218–227.

Heckathorn, D.D., Cameron, C.J., 2017. Network sampling: from snowball and multiplicity to respondent-driven sampling. Annu. Rev. Sociol. 43, 101–119.

Heidt, T., Sager, H.B., Courties, G., Dutta, P., Iwamoto, Y., Zaltsman, A., Von Zur Muhlen, C., Bode, C., Fricchione, G.L., Denninger, J., 2014. Chronic variable stress activates hematopoietic stem cells. Nat. Med. 20, 754.

Hirzalla, F., Zoonen, L. van, 2011. Beyond the online/offline divide: how youth's online and offline civic activities converge. Soc. Sci. Comput. Rev. 29, 481–498. https://doi.org/10.1177/0894439310385538.

Hood, M., Creed, P.A., Mills, B.J., 2018. Loneliness and online friendships in emerging adults. Personal. Individ. Differ., Examining Personal. Individ. Differ. Cyber 133, 96–102. https://doi.org/10.1016/j.paid.2017.03.045.

Hopmeyer, A., Terino, B., Adamczyk, K., Corbitt Hall, D., DeCoste, K., Troop-Gordon, W., 2022. The lonely collegiate: an examination of the reasons for loneliness among emerging adults in college in the Western United States and West-Central Poland. Emerg. Adulthood 10, 237–248. https://doi.org/10.1177/2167696820966110.

Hughes, M.E., Waite, L.J., Hawkley, L.C., Cacioppo, J.T., 2004. A short scale for measuring loneliness in large surveys. Res. Aging 26, 655–672.

Hwang, T.-J., Rabheru, K., Peisah, C., Reichman, W., Ikeda, M., 2020. Loneliness and social isolation during the COVID-19 pandemic. Int. Psychogeriatr. 32, 1217–1220.

Johannes, N., Vuorre, M., Przybylski, A.K., 2020. Video game play is positively correlated with well-being. PsyArXiv. https://doi.org/10.31234/osf.io/qrjza.

Jones, C., Scholes, L., Johnson, D., Katsikitis, M., Carras, M.C., 2014. Gaming well: links between videogames and flourishing mental health. Front. Psychol. 5, 260.

Kardefelt-Winther, D., 2014. A conceptual and methodological critique of internet addiction research: towards a model of compensatory internet use. Comput. Hum. Behav. 31, 351–354.

Kasar, K.S., Karaman, E., 2021. Life in lockdown: social isolation, loneliness and quality of life in the elderly during the COVID-19 pandemic: a scoping review. Geriatr. Nurs. 42, 1222–1229.

Keyes, C.L., 2009. Brief description of the mental health continuum short form (MHC-SF).

Keyes, C.L.M., 1998. Social well-being. Soc. Psychol. Q. 61, 121–140. https://doi.org/10.2307/2787065.

Killgore, W.D., Cloonan, S.A., Taylor, E.C., Lucas, D.A., Dailey, N.S., 2020. Loneliness during the first half-year of COVID-19 Lockdowns. Psychiatry Res. 294, 113551.

Kitayama, S., Akutsu, S., Uchida, Y., Cole, S.W., 2016. Work, meaning, and gene regulation: findings from a Japanese information technology firm. Psychoneuroendocrinology 72, 175–181.

Kohrt, B.A., Worthman, C.M., Adhikari, R.P., Luitel, N.P., Arevalo, J.M., Ma, J., McCreath, H., Seeman, T.E., Crimmins, E.M., Cole, S.W., 2016. Psychological resilience and the gene regulatory impact of posttraumatic stress in Nepali child soldiers. Proc. Natl. Acad. Sci. USA 113, 8156–8161.

Lamers, S.M.A., Westerhof, G.J., Bohlmeijer, E.T., Klooster, P.M., ten, Keyes, C.L.M., 2011. Evaluating the psychometric properties of the mental health Continuum-Short Form (MHC-SF). J. Clin. Psychol. 67, 99–110. https://doi.org/10.1002/jclp.20741.

Lim, M., Eres, R., Peck, C., 2019. The young Australian loneliness survey: Understanding loneliness in adolescence and young adulthood.

Luhmann, M., Hawkley, L.C., 2016. Age differences in loneliness from late adolescence to oldest old age. Dev. Psychol. 52, 943–959. https://doi.org/10.1037/dev0000117.

Matthews, T., Danese, A., Caspi, A., Fisher, H.L., Goldman-Mellor, S., Kepa, A., Moffitt, T. E., Odgers, C.L., Arseneault, L., 2019. Lonely young adults in modern Britain: findings from an epidemiological cohort study. Psychol. Med. 49, 268–277. https://doi.org/10.1017/S0033291718000788.

Mattos dos Santos, R., 2020. Isolation, social stress, low socioeconomic status and its relationship to immune response in Covid-19 pandemic context. Brain Behav. Immun. Health 7, 100103. https://doi.org/10.1016/j.bbih.2020.100103.

McDade, T.W., M. Ross, K., Fried, L., Arevalo, R., Ma, J.M., Miller, J., Cole, S.W, G.E., 2016. Genome-wide profiling of RNA from dried blood spots: Convergence with

bioinformatic results derived from whole venous blood and peripheral blood mononuclear cells. Biodemography Soc. Biol. 62, 182–197.
McKim, D.B., Yin, W., Wang, Y., Cole, S.W., Godbout, J.P., Sheridan, J.F., 2018. Social stress mobilizes hematopoietic stem cells to establish persistent splenic myelopoiesis. Cell Rep. 25, 2552–2562.
Nelson-Coffey, S.K., Fritz, M.M., Lyubomirsky, S., Cole, S.W., 2017. Kindness in the blood: a randomized controlled trial of the gene regulatory impact of prosocial behavior. Psychoneuroendocrinology 81, 8–13.
Nowland, R., Necka, E.A., Cacioppo, J.T., 2017. Loneliness and social internet use: pathways to reconnection in a digital world. Perspect. Psychol. Sci. https://doi.org/10.1177/1745691617713052.
Palgi, Y., Shrira, A., Ring, L., Bodner, E., Avidor, S., Bergman, Y., Cohen-Fridel, S., Keisari, S., Hoffman, Y., 2020. The loneliness pandemic: loneliness and other concomitants of depression, anxiety and their comorbidity during the COVID-19 outbreak. J. Affect. Disord. 275, 109.
Petrillo, G., Capone, V., Caso, D., Keyes, C.L., 2015. The mental health continuum–short form (MHC–SF) as a measure of well-being in the Italian context. Soc. Indic. Res. 121, 291–312.
Petry, N.M., Rehbein, F., Gentile, D.A., Lemmens, J.S., Rumpf, H.-J., Mössle, T., Bischof, G., Tao, R., Fung, D.S., Borges, G., et al., 2014. An international consensus for assessing internet gaming disorder using the new DSM-5 approach. Addiction 109, 1399–1406.
Powell, N.D., Sloan, E.K., Bailey, M.T., Arevalo, J.M., Miller, G.E., Chen, E., Kobor, M.S., Reader, B.F., Sheridan, J.F., Cole, S.W., 2013. Social stress up-regulates inflammatory gene expression in the leukocyte transcriptome via β-adrenergic induction of myelopoiesis. Proc. Natl. Acad. Sci. USA 110, 16574–16579.
Reissmann, A., Hauser, J., Stollberg, E., Kaunzinger, I., Lange, K.W., 2018. The role of loneliness in emerging adults' everyday use of facebook – an experience sampling approach. Comput. Hum. Behav. 88, 47–60. https://doi.org/10.1016/j.chb.2018.06.011.
Ryff, C.D., Singer, B.H., 2008. Know thyself and become what you are: a eudaimonic approach to psychological well-being. J. Happiness Stud. 9, 13–39.
Schiano, D.J., Nardi, B., Debeauvais, T., Ducheneaut, N., Yee, N., 2014. The "lonely gamer" revisited. Entertain. Comput. 5, 65–70.
Shah, S.G.S., Nogueras, D., Woerden, H.C., van, Kiparoglou, V., 2020. The COVID-19 pandemic: a pandemic of lockdown loneliness and the role of digital technology. J. Med. Internet Res. 22, e22287 https://doi.org/10.2196/22287.
Slater, D., 2002. Social relationships and identity online and offline. Handb. N. Media.: Soc. Shap. Conséq. ICTs 533–546.
Snodgrass, J.G., Lacy, M.G., Cole, S.W., 2022. Internet gaming, embodied distress, and psychosocial well-being: A syndemic-syndaimonic continuum. Social Science & Medicine 295. https://doi.org/10.1016/j.socscimed.2019.112728.
Snodgrass, J.G., Bagwell, A., Patry, J.M., Dengah II, H.J.F., Smarr-Foster, C., Van Oostenburg, M., Lacy, M.G., 2018a. The partial truths of compensatory and poor-get-poorer internet use theories: more highly involved videogame players experience greater psychosocial benefits. Comput. Hum. Behav. 78, 10–25.
Snodgrass, J.G., Dengah II, H.J.F., Lacy, M.G., Else, R.J., Polzer, E.R., Arevalo, J.M., Cole, S.W., 2018b. Social genomics of healthy and disordered internet gaming. Am. J. Hum. Biol. 30, e23146.
Snodgrass, J.G., Lacy, M.G., Dengah II, H.J.F., Polzer, E.R., Else, R.J., Arevalo, J.M.G., Cole, S.W., 2019. Positive mental well-being and immune transcriptional profiles in highly involved videogame players. Brain, Behav., Immun. 82, 84–92.
Tasso-M20 [WWW Document], 2020. Tasso Inc. URL ⟨https://www.tassoinc.com/tasso-m20⟩ (accessed 12.23.20).
Towner, E., Ladensack, D., Chu, K., Callaghan, B., 2021. Welcome to My Zoom Party - Virtual Social Interaction, Loneliness, and Well-Being Among Emerging Adults Amid the COVID-19 Pandemic. https://doi.org/10.31234/osf.io/2ghtd.
Turkle, S., 2012. Alone Together: Why We Expect More from Technology and Less from Each Other. Basic books,.
Twenge, J.M., Haidt, J., Joiner, T.E., Campbell, W.K., 2020. Underestimating digital media harm. Nat. Hum. Behav. 4, 346–348.
Van Tilburg, T.G., Steinmetz, S., Stolte, E., van der Roest, H., de Vries, D.H., 2021. Loneliness and mental health during the COVID-19 pandemic: a study among Dutch older adults. J. Gerontol.: Ser. B 76, e249–e255.
Wickens, C.M., McDonald, A.J., Elton-Marshall, T., Wells, S., Nigatu, Y.T., Jankowicz, D., Hamilton, H.A., 2021. Loneliness in the COVID-19 pandemic: associations with age, gender and their interaction. J. Psychiatr. Res. 136, 103–108.
Wiederhold, B.K., 2020a. Using social media to our advantage: alleviating anxiety during a pandemic. Cyber, Behav., Soc. Netw. 23, 197–198. https://doi.org/10.1089/cyber.2020.29180.bkw.
Wiederhold, B.K., 2020b. Teletherapy: the new norm. Cyber, Behav., Soc. Netw. 23, 655–656. https://doi.org/10.1089/cyber.2020.29196.editorial.
Wong, A., Ho, S., Olusanya, O., Antonini, M.V., Lyness, D., 2021. The use of social media and online communications in times of pandemic COVID-19. J. Intensive Care Soc. 22, 255–260.