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# Social genomics of healthy and disordered internet gaming

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## Abstract

**Objectives:** To combine social genomics with cultural approaches to expand understandings of the somatic health dynamics of online gaming, including in the controversial nosological construct of internet gaming disorder (IGD).

**Methods:** In blood samples from 56 U.S. gamers, we examined expression of the conserved transcriptional response to adversity (CTRA), a leukocyte gene expression profile activated by chronic stress. We compared positively engaged and problem gamers, as identified by an ethnographically developed measure, the Positive and Negative Gaming Experiences Scale (PNGE-42), and also by a clinically derived IGD scale (IGDS-SF9).

**Results:** CTRA profiles showed a clear relationship with PNGE-42, with a substantial linkage to offline social support, but were not meaningfully associated with disordered play as measured by IGDS-SF9.

**Conclusions:** Our study advances understanding of the psychobiology of play, demonstrating via novel transcriptomic methods the association of negatively experienced internet play with biological measures of chronic threat, uncertainty, and distress. Our findings are consistent with the view that problematic patterns of online gaming are a proxy for broader patterns of biopsychosocial stress and distress such as loneliness, rather than a psychiatric disorder *sui generis*, which might exist apart from gamers' other life problems. By confirming the biological correlates of certain patterns of internet gaming, culturally-sensitive genomics approaches such as this can inform both evolutionary theorizing regarding the nature of play, as well as current psychiatric debates about the appropriateness of modeling distressful gaming on substance addiction and problem gambling.

## 1 | INTRODUCTION

Internet gaming is an expanding international phenomenon, with popular games counting millions of players, well-developed fandoms, and even substantial e-sports leagues with million dollar payoffs (Taylor, 2012). Such games are not just entertaining hobbies; play in online worlds powerfully impacts gamers' emotional lives and social identities (Nardi, 2010; Snodgrass et al., 2018; Yee, 2014). Gamers' passion for play brings cognitive, emotional, motivational, and social benefits (Granic, Lobel, & Engels, 2014). But some gamers go online to escape offline dysphoric moods and problematic relationships, which can alleviate distress, but can also become obsessive and

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compulsive, creating problems resembling addiction (Kardefelt-Winther, 2014b; Snodgrass, Dengah, & Lacy, 2014).

Neurobiological and ethological research suggests that play is an evolutionarily conserved basic behavioral module, manifested among mammalian species from mice to chimpanzees to humans (Panksepp, 2004). Whatever its form, play allows for feigned and typically safe pursuit of social and other rewards, and has been linked to brain circuitry involved in the learning and development of key cognitive and emotional skills, including those related to social dominance and cooperation (Panksepp, 2007, 2010; Pellis & Pellis, 2007). Enjoyable and satisfying, human play activates and is partially organized by ancient mammalian reward systems such as the mesolimbic dopamine pathway, which coordinates activity between deep brain structures like the ventral striatum (related to appetitive motivation and the acquisition of habit), the mid-brain ventral tegmental area (connected to emotion and motivation areas such as the amygdala and nucleus accumbens), and higher planning in the prefrontal cortex (which balances future and present wants) (Burgdorf, Wood, Kroes, Moskal, & Panksepp, 2007; Cole, Yoo, & Knutson, 2012; Cox et al., 1984; Koepp et al., 1998; Siviy & Panksepp, 2011). Play appears to have evolved as a system promoting the pursuit and acquisition of evolutionarily adaptive behaviors and experiences in the context of social groups (Panksepp, 2004; Pellis & Pellis, 2007). This encompasses motivations to seek and discover social rewards as ends in themselves, key themes in play in general and notably in contemporary online gaming, which, rendered playful, are enjoyable and thus more likely to be pursued (Dengah, Snodgrass, Else, & Polzer, 2018; Panksepp, 2010). Play's pleasures focus attention on the things that count from participants' points of view, allowing through simulation social animals to effectively learn the social and other boundaries and possibilities of their lives (Bekoff, 1984; Graham & Burghardt, 2010; LaFreniere, 2011). However, linked to brain reward centers, play has the potential to become overly absorbing, so that it competes with rather than promotes desirable life goals and behaviors (Panksepp, 2010; Panksepp, Knutson, & Burgdorf, 2002). In these cases, play fosters maladaptive forms of learning that result in obsessive, compulsive, and addictive seeking behavior (Kelley & Berridge, 2002; Panksepp et al., 2002). Play then becomes a source of stress rather than pleasure, with the potential to chronically activate psychobiological stress response systems such as the autonomic nervous system, with stress implicated as both a cause and effect of addiction in general (Kreek, Nielsen, Butelman, & LaForge, 2005; Pohorecky, 1991; Sinha, 2008), as well as in internet and gaming addictions more specifically (Leung, 2007; Lu, Wang, & Huang, 2010; Mauri, Cipresso, Balgera, Villamira, & Riva, 2011; Snodgrass et al., 2016; Snodgrass, Lacy, et al., 2014; Snodgrass, Lacy, Dengah, Fagan, & Most, 2011; Yan, Li, & Sui, 2014).

As a significant form of contemporary human play, internet gaming should share the neurobiological circuitry and evolutionary significance of older general mammalian and human forms of play, along with similar maladaptive addictive potential. We thus thought that certain patterns of internet play might manifest in somatic stress physiology. Specifically, we anticipated that internet gamers who experienced their gameplay as more negative or addictive would also show increased expression of a stress-induced gene expression profile known as the "conserved transcriptional response to adversity" (CTRA) (Cole, 2014). 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; Powell et al., 2013), and involves up-regulated expression of genes involved in inflammation and down-regulated expression of genes involved in interferon/anti-viral responses and antibody production (Cole, 2017; Cole, 2014). This profile appears to constitute an evolutionarily conserved molecular defense program, as it is observed across a wide range of species from fish to primates (Cole, Conti, et al., 2012; Heidt et al., 2014; Korytář et al., 2016; Powell et al., 2013; Snyder-Mackler et al., 2016), and in a range of adverse environmental conditions ranging from social isolation (Cole et al., 2007; Cole, Capitanio, et al., 2015; Cole, Levine, et al., 2015) to depression and anxiety (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008), low social status (Powell et al., 2013; Snyder-Mackler et al., 2016), social loss (Miller et al., 2008, 2014; O'Connor, Schultze-Florey, Irwin, Arevalo, & Cole, 2014), and trauma (Kohrt et al., 2016). One advantage of examining CTRA gene expression is that, unlike many other stress-related biomarkers, the cellular and molecular processes underlying the CTRA are directly involved in the long-term development of chronic illnesses that represent the major sources of contemporary mortality (i.e., cardiovascular disease, cancer, and neurodegenerative diseases) (Cole, 2014; Finch, 2010).

To further understanding of behavioral problems from a simultaneous psychobiological and ethnographically sensitive perspective, we examined CTRA gene expression profiles in a sample of U.S. internet gamers ($N = 56$) selected so that half of them were playing in apparently functional and healthy manners, and half were experiencing gaming-related problems. To assess their internet gaming-related experience, we relied principally on a scale we developed and ethnographically validated in earlier research, the Positive and Negative Gaming Experiences Scale (PNGE-42), which assesses the relative balance of positive and negative gaming experiences identified as important to online gamers according to their own cultural frames of reference (Snodgrass et al., 2017). Our PNGE-42 scale assessing gaming experiences ethnographically extends Yee's well-established understanding of online gaming involvement, with *achievement*,

*social*, and *immersion* motivations shaping online play's pleasures and perils (Yee, 2006a, 2006b, 2006c), a scheme based on foundational work by Bartle and further validated in other research (Bartle, 1996; Charlton & Danforth, 2007; Snodgrass et al., 2012; Snodgrass, Dengah, Lacy, & Fagan, 2013). *We hypothesized that blood samples from members of our more positively proportional PNGE-42 group (N = 28) would show less expression of the CTRA profile compared to those from individuals in the group having fewer positive gaming experiences (also N = 28)* (H1). (By "positively proportional," we mean the extent to which players' ratings of their positive experiences associated with internet gaming predominate over their negative experiences. Here, a higher score on our measure reflects fewer gaming-related problems. For a full description of the PNGE-42 measure, including all 42 of its items, see Supporting Information Appendix S1: Positive and Negative Gaming Experiences (PNGE-42).)

Of note, concerns about dysfunctional aspects of gaming are reflected in proposals from both the American Psychiatric Association (APA) and the World Health Organization (WHO) to include variations of "gaming disorder" as formal psychiatric diagnoses in their nosological manuals (American Psychiatric Association, 2013; World Health Organization, n.d.). The APA has introduced "internet gaming disorder" (IGD) as a nonsubstance addiction akin to gambling in a research appendix in the 5th edition of the Diagnostic and Statistical Manual (DSM-5) (American Psychiatric Association, 2013; Petry et al., 2014). More recently, the WHO has preliminarily proposed "gaming disorder"—a subset of disorders due to addictive behaviors—for the next (11th) edition of the International Classification of Diseases (ICD) (Aarseth et al., 2017; World Health Organization, 2017). Proposed IGD diagnostic categories from the APA and WHO do fit with researchers' agreement that a small percentage of videogame players (~2%-5%) experience serious gaming-related problems (Pontes, Kiraly, Demetrovics, & Griffiths, 2014), including the inability to limit their play despite negative consequences in their lives, which can produce functional impairment and psychological distress (Aarseth et al., 2017; Petry et al., 2014).

Attentive to psychiatric formulations of gaming-related distress, we also assessed our respondents' play experience using a clinically derived IGD instrument, the IGDS-SF9 (Pontes & Griffiths, 2015). By also examining IGD social genomics, our analysis allows us to speak even more directly to current APA, WHO, and scholarly proposals that model dysfunctional and distressful gaming on substance addiction and problem gambling symptomology (Aarseth et al., 2017; American Psychiatric Association, 2013; Griffiths et al., 2015; Petry et al., 2014; World Health Organization, 2017, n.d.). *We anticipated that blood samples from individuals crossing IGD diagnostic thresholds (N = 3) would show greater CTRA compared to samples from those below that threshold (N = 53)* (H2).

Finally, some scholars stress that problem gaming should be understood as a response to life problems rather than as a psychiatric disorder *sui generis* (Kardefelt-Winther, 2014a; Snodgrass, Lacy, et al., 2014). Anthropologically-minded scholars suggest framing emotional distress in particular cultural contexts via locally salient "idioms of distress" (Nichter, 1981), "socially and culturally resonant means of experiencing and expressing distress in local worlds" (Nichter, 2010, p. 405), which the PNGE-42 captures. We wondered if problematic gaming patterns might be a behavioral idiom used to express social suffering such as loneliness. As such, gaming-related problems might represent a rather familiar response to psychosocial problems such as social isolation, whose health (and CTRA) effects are well established, rather than a new psychiatric disorder *per se* (Cacioppo, Cacioppo, Capitanio, & Cole, 2015; Cole, Capitanio, et al., 2015; Cole, Levine, et al., 2015). Supporting such an idea, research both in the United States (Snodgrass, Lacy, et al., 2014; Snodgrass, Dengah, et al., 2014; Snodgrass, Lacy, Dengah, & Fagan, 2011; Weinstein et al., 2015) and also in East Asia (Jang, Hwang, & Choi, 2008; Ko, Yen, Yen, Chen, & Chen, 2012; Wang, Ho, Chan, & Tse, 2015) shows that problem gaming is comorbid with pre-existing mental illness like depression and anxiety, as well as with stress and a general lack of satisfaction and success in life. It has also been found that those lacking social support in particular—e.g., lonely persons feeling they lack community—tend to use the internet more problematically (Caplan, Williams, & Yee, 2009). This has led some to suggest that problem internet use itself might be a response to a lack of meaningful social relations and support, with online gamers, for example, looking to virtual communities to fill social voids (Lee & Stapinski, 2012; Longman, O'Connor, & Obst, 2009). Here, intensive videogaming could be considered a new technological and culturally sanctioned "idiom" through which gamers experience and communicate to others their life distress—such as the experience of social isolation—which can either further magnify or help to resolve gamers' life problems (Kardefelt-Winther, 2014a, 2014b; Snodgrass, Lacy, et al., 2014; Snodgrass, Dengah, et al., 2014).

With these issues in mind, we further collected data on social isolation and loneliness from our gamer respondents, which allowed us to explore connections between loneliness and other social support factors and the psychosocial pleasures and risks of online gaming (Kim, LaRose, & Peng, 2009; Nowland, Necka, & Cacioppo, 2018; Reer & Krämer, 2017; Schiano, Nardi, Debeauvais, Ducheneaut, & Yee, 2014; Snodgrass et al., 2018). Specifically, we examined how healthy and unhealthy gamers' preexisting mental health problems (Ferguson, Coulson, & Barnett, 2011; Mentzoni et al., 2011), distinctive patterns of heavy use (assessed by

hours played per day) (Baggio et al., 2016; Charlton & Danforth, 2010; Demetrovics & Király, 2016; Griffiths, 2010), and social isolation and loneliness (Kim et al., 2009; Nowland et al., 2018; Schiano et al., 2014; Snodgrass et al., 2018) might help explain any CTRA differences seen between our observed gaming experiences groups. Centrally, we anticipated that *offline* social support in particular would be determinant in these analyses, based on prior research conducted by us and others (Snodgrass et al., 2018; Snodgrass et al., 2011; Trepte, Reinecke, & Juechems, 2012; Valkenburg & Peter, 2009). *We expected that offline compared to online social support might help explain observed CTRA differences, with blood samples from persons experiencing less offline social support in particular manifesting more of the characteristic CTRA profile* (H3).

## 2 | METHODS

### 2.1 | Participants

We studied a sample of internet gamers playing in an apparently functional manner compared to others who gamed more problematically. Specifically, from among the respondents to a prior survey of ours ($N = 404$), we recruited persons from Colorado and Utah who scored in the top and bottom quartiles of our previously developed Positive and Negative Gaming Experiences Scale (PNGE-42) (Snodgrass et al., 2017). They were asked to provide blood and to meet with us for additional interviewing. Thus, participants for this study were obtained through a two stage process: first, from local internet gaming clubs, gaming forums, and other networks of ethnographic informants, we recruited persons from two university communities in Utah and Colorado to complete an online survey of gamer experiences between January 2016 and October 2016. We obtained 473 total respondents to our web survey, of which 404 were local (214 from Colorado and 190 from Utah). Next, to obtain the transcriptome data analyzed here, we invited all local persons whose survey responses placed them in the top or bottom quartiles of our PNGE-42 scale to provide blood and to meet with us for additional face-to-face interviewing. Described in more detail below, the PNGE-42 measured the extent to which a respondent showed a balanced as opposed to problematic engagement with internet game play. We met and drew blood from a total of 58 persons, 28 persons with low scores on this measure (PNGE-42 $\leq 14$) and 30 with high scores (PNGE-42 $\geq 37$) (two of the latter were later eliminated due to inadequate CTRA profiles, which we explain below). Thus, our study sample contained two groups selected so as to differ distinctly with respect to possibly dysfunctional internet game play. All participants provided informed consent prior to participation, and all procedures were approved by the Institutional Review Board of Colorado State University.

### 2.2 | Procedure

Potential participants were first contacted via email, and arrangements were made for their continued participation in the study. Researchers conducted the blood collection and in-person interviews at a time and location of the participant's choosing (e.g., homes, libraries, offices, Snodgrass's and Dengah's respective CSU and USU research labs).

### 2.3 | Blood spot collection protocol

Standard blood spot collection procedures were used (McDade, Williams, & Snodgrass, 2007). Researchers used lancets to prick the ring or middle fingertips, and draw approximately 5 drops of blood (~50 μL) that were collected onto Whatman (#903) filter paper cards. The blood was allowed to dry onto the filter paper before being stored in an airtight plastic bag, with a desiccant to complete the drying process. Blood spot samples were stored in a secure freezer (–30°C) until being shipped to the UCLA Social Genomics Core Laboratory for gene expression analysis.

### 2.4 | Transcriptome profiling

We conducted genome-wide transcriptional profiling of dried blood spots using methods previously established 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 filter papers using a standard RNA stabilization buffer (Qiagen RLT), extracted using standard methods (Qiagen RNeasy), converted to fluorescent cDNA (NuGEN PicoSL) and hybridized to Illumina Human HT-12 v4 BeadArrays following the manufacturer's standard protocol in the UCLA Neuroscience Genomics Core Laboratory. Two participants' samples yielded insufficient RNA for analysis. The remaining 56 samples were assayed in a single batch and yielded valid results according to standard quality assurance methods (e.g., median probe fluorescence intensity >80 units). The microarray-based transcriptome profiling approach used here did not require any normalization to a specific internal housekeeping control because the quantile-based data normalization employed at the outset of data analysis (see below) standardizes total assayed RNA levels across samples at the level of the whole transcriptome (Bolstad, Irizarry, Åstrand, & Speed, 2003).

### 2.5 | Other measures

Most measurements other than the transcriptome data were collected as part of participants' initial online survey, with

additional information (such as body mass index [BMI]) collected in face-to-face meetings along with the blood-draw.

### 2.5.1 | Positive and negative gaming experiences (PNGE-42)

As discussed, as a method to determine whether individuals were engaged in more psychosocially healthy as opposed to disordered modes of internet game play, we developed and administered our own Positive and Negative Gaming Experience measure (PNGE-42), which we describe in more detail elsewhere (Snodgrass et al., 2017). The PNGE-42 we use in this study contains two 21-item positive and negative consequence scales, each with six psychosomatic impact items (three more psychologically oriented and three more somatic), six behavioral consequences questions (such as the game producing positive structure or by contrast boring and potentially compulsive routine), six social outcomes (such as gaming providing satisfying community or, instead, creating feelings of social isolation), and three achievement-oriented items (such as online play producing satisfying feelings of accomplishment or conversely feeling more like a "dead-end job") (Snodgrass et al., 2017). Importantly, and as noted earlier, a *higher* score on PNGE-42—as reflecting more positive and fewer negative gaming experiences—shows *less* gaming-related distress. (Again, for further detail, consult Supporting Information Appendix S1: Positive and Negative Gaming Experiences (PNGE-42).)

### 2.5.2 | IGDS-SF9 (PIU)

As a further measure of problem gaming experiences, we used the 9-item Internet Gaming Disorder Scale, short form (IGDS-SF9) (Pontes & Griffiths, 2015). This scale was produced to represent the clinical dimensions of internet gaming disorder as outlined by the DSM-5, including preoccupation, withdrawal, tolerance, failed control attempts, loss of outside interests, excessive use, deception, escapism, and destructive effects. The nine items are measured along a 5-point Likert Scale, to measure frequency of occurrence over the past year (1 ("Never"), 2 ("Rarely"), 3 ("Sometimes"), 4 ("Often"), and 5 ("Very Often"). The items are summed, providing a possible range from 9 to 45. For classification purposes, individuals who score a 36 or above (averaging a response of "often" to all 9 items) can be regarded as a "disordered" gamer (Pontes & Griffiths, 2015). This scale has been widely used, and has demonstrated good internal reliability and validity (Pontes & Griffiths, 2015). In our study sample, this scale had a Cronbach's alpha of 0.88, and was positively correlated with total gaming hours ($r = 0.44$, $P < .005$), and negatively correlated with our own PNGE-42 scale ($r = -0.23$, $P = .077$). In contrast to our PNGE-42, higher scores on the clinical IGDS-SF9 reflect *greater* gaming-related distress.

Besides using IGDS-SF9 as a continuous variable in analyses presented here, we also coded it into a binary measure so as to identify individuals above and below the suggested diagnostic threshold of 36 for disorder. We also used it as a binary variable divided at 28, a comparison chosen because respondents scoring at this level or higher expressed significant gaming-related distress symptomology in our qualitative interviews. While this latter cut-point is lower than the 36 or above diagnostic threshold that the developers of this scale suggest, we decided it was advisable to also compare respondents at or above this break, given our study's ethnographic aim to remain true to respondents' expressed experiences.

### 2.5.3 | Subjective well-being

Subjective well-being was measure via the 3-item hedonia dimension (happiness, interest in life, life satisfaction) of the Mental Health Continuum-Short Form (MHC-SF), a measure of positive mental health rated along a 6-point Likert scale (1 = 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) (Keyes, 2009). Hedonic well-being served as a control variable, reflecting pre-existing mental health, and theoretically accounting for gamers who may use online behavior to help compensate for their offline lives (Kardefelt-Winther, 2014a; Snodgrass, Lacy, et al., 2014). Our 3-item subjective well-being showed good internal consistency with a Cronbach's alpha of 0.85.

### 2.5.4 | Online and offline social support

For social support, we adapted a 4-item version of a previously validated "Interpersonal Support Evaluation List" (ISEL), which asked respondents if they had people they could turn to online and offline for help with their problems, for advice, conversation, or with whom they simply enjoyed spending time (Cohen & Hoberman, 1983). This created two 4-item scales, one for online support, the other for offline support, with items in each rated along a 5-point scale (1 ("Strongly Disagree"), 2 ("Disagree"), 3 ("Neutral"), 4 ("Agree"), and 5 ("Strongly Agree"). Each scale was summed separately, providing for a possible range between 4 and 20, with higher values indicating greater perceived social support. The online social support showed good internal consistency with a Cronbach's alpha of 0.84. Similarly, offline social support had an alpha of 0.91. This item was treated as a continuous variable in statistical analyses.

### 2.5.5 | Covariates

Standard covariates were collected from participants after the blood draw, including age, gender, and state of residence (Utah = 0, Colorado = 1). Additionally, participants reported

their average gaming hours per day (0–1 hours, 1–2, 2–3, 3–4, 4–5, 5–6, 6 or more hours). Estimated BMI was collected through self-reported height and weight. Alcohol consumption was collected as recalled reports of daily consumption during an average week, and was coded as either more than two per day, or fewer. Given our relatively limited sample size, it was advisable to limit the number of covariates in linear model analyses. As such, we excluded location, age, and other indicators, as they did not show significant bivariate correlations to either of our two key predictor scales (PNGE-42 and IGDS-SF9) or to CTRA.

### 2.6 | Statistical analysis

Following the approach of previous studies, gene expression values were quantile-normalized (Bolstad et al., 2003) and log2-transformed, and used as response variables in linear model analyses quantifying the associations of gene expression with key predictor variables. All analyses reported here included controls for an established set of potential confounders, including participant gender, BMI, and history of heavy alcohol consumption. Initial model specification tests also examined potential effects of age and location; these variables showed no significant association with CTRA gene expression in this sample and were subsequently omitted from future analyses to minimize the risk of model overfitting given the limited sample size available. The primary outcome analyzed in this study was a contrast computed over 53 previously specified CTRA indicator genes (Fredrickson et al., 2013, 2015), including 19 pro-inflammatory genes (*IL1A, IL1B, IL6, IL8, TNF, PTGS1, PTGS2, FOS, FOSB, FOSL1, FOSL2, JUN, JUNB, JUND, NFKB1, NFKB2, REL, RELA, RELB*) weighted +1 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 (*IGJ, IGLL1, IGLL3*) weighted −1 as inverse indicators (Fredrickson et al., 2013, 2015). As often occurs with the limited RNA mass derived from dried bloodspots, several CTRA indicator genes were missing in one or more samples. This resulted in list-wise deletion of data on *IL1B*, *IFI15*, and *IFITM1*, leaving a CTRA indicator contrast defined over the remaining 50 available indicator genes. Contrast scores were tested for statistically significant difference from the null hypothesis value of 0 association using standard errors derived from bootstrap resampling of vectors of linear model residuals (accounting for any correlation among residuals across genes). Secondary analyses examined the cellular origins of all genes showing > 1.25-fold differential expression, using Transcript Origin Analysis as previously described (Cole, Hawkley, Arevalo, & Cacioppo, 2011).

Effect sizes for the resulting linear model coefficients (e.g., difference in predicted gene expression by IGDS-SF9, PNGE-42, Offline Social Support) were graphed as the range-spanning magnitude of difference in predicted CTRA indicator gene abundance over a standardized range of scores. The statistical significance level was set at $p < 0.05$, and analyses followed established statistical guidelines in controlling for multiple comparisons in exploratory analyses of many related hypotheses (e.g., correlations among covariates and IGD-9/PNGE-42) but not in analyses of distinct primary substantive hypotheses (e.g., testing associations between IGD-9/PNGE-42 and CTRA contrast scores).

## 3 | RESULTS

Among the 58 individuals from whom we collected blood samples, 56 yielded valid transcriptome profiles and had data available for all indicator variables analyzed. Our sample was largely male (64%), typically early 20s (range 18–37), white (∼90%), employed full or part-time (∼75%), married or in a committed relationship (63%), and with at least some college education (most, about 80%, were currently students), which parallels other published profiles of U.S. internet gamers showing them to be typically male, of European descent, and educated (Yee, 2006b).

Table 1 shows the frequency of key variables considered in our analysis, first for the sample as a whole and then separately for our study's healthy versus problem gamer groups (as defined in three different ways). Summary statistics are also shown for control variables showing significant relationships with our key predictors and/or CTRA outcome. A key comparison appears in the two columns labeled "PNGE-High/Low," which contrasts the group of gamers who played in a more vs. less psychosocially healthy manner ($N = 28$ in each group), according to our 42-item ethnographically-derived scale (Snodgrass et al., 2017). Persons in the PNGE-High group all had PNGE-42 scores ≥37, while those in the PNGE-Low group had scores ≤14 (i.e., the two groups were drawn from survey respondents scoring in the top and bottom quartiles of that gaming experience measure). The next two results columns show characteristics for gamers falling either below ($N = 53$) or at or above ($N = 3$) the suggested clinical cut-point of 36 on the IGDS-SF9 (to be classified as playing in a "disordered" fashion, respondents would need to mark on average four out of five on each of the nine symptoms' Likert items, claiming to have experienced each of those symptoms "often" or "very often") (Pontes & Griffiths, 2015). Finally, the last two results columns are for respondents above ($N = 48$) or below ($N = 8$) a score of 28 on the IGDS-SF9, an additional comparison chosen because respondents scoring at this level expressed significant gaming-related distress symptomology in our qualitative

**TABLE 1** Group differences on key variables: More/less psychosocially healthy gaming groups (PNGE-42 High/Low); Healthy vs. disordered gaming groups (clinical cut-point of ≥36); Healthy vs. disordered gaming groups (ethnographic cut-point of ≥28)

| Factor<br>N | Level | Total Sample<br>56 | PNGE-High<br>28 | PNGE-Low<br>28 | *P*-value[a] | IGDS-SF9 < 36<br>53 | IGDS-SF9 ≥ 36<br>3 | *P*-value[b] | IGDS-SF9 < 28<br>48 | IGDS-SF9 ≥ 28<br>8 | *P*-value[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Location | UT | 23 (41%) | 10 (36%) | 13 (46%) | .42 | 22 (42%) | 1 (33%) | .78 | 21 (44%) | 2 (25%) | .32 |
| | CO | 33 (59%) | 18 (64%) | 15 (54%) | | 31 (58%) | 2 (67%) | | 27 (56%) | 6 (75%) | |
| 1 = Male | 0 | 20 (36%) | 9 (32%) | 11 (39%) | .58 | 19 (36%) | 1 (33%) | .93 | 18 (38%) | 2 (25%) | .49 |
| | 1 | 36 (64%) | 19 (68%) | 17 (61%) | | 34 (64%) | 2 (67%) | | 30 (63%) | 6 (75%) | |
| 1 = Two or more drinks per day | 0 | 52 (93%) | 25 (89%) | 27 (96%) | .30 | 49 (92%) | 3 (100%) | .62 | 44 (92%) | 8 (100%) | .40 |
| | 1 | 4 (7%) | 3 (11%) | 1 (4%) | | 4 (8%) | 0 (0%) | | 4 (8%) | 0 (0%) | |
| Age, mean (SD) | | 23.79 (4.15) | 23.29 (4.09) | 24.29 (4.23) | .37 | 23.85 (4.26) | 22.67 (1.15) | .64 | 23.83 (4.07) | 23.50 (4.93) | .84 |
| BMI, mean (SD) | | 24.38 (4.56) | 24.48 (4.52) | 24.28 (4.68) | .87 | 24.12 (4.41) | 29.00 (5.74) | .071 | 24.42 (4.25) | 24.15 (6.49) | .88 |
| Hours gaming/day, mean (SD) | | 2.96 (1.69) | 3.29 (1.51) | 2.64 (1.83) | .16 | 2.85 (1.62) | 5.00 (2.00) | .031 | 2.67 (1.51) | 4.75 (1.75) | <.001 |
| Hedonia, mean (SD) | | 14.32 (2.39) | 14.46 (1.97) | 14.18 (2.78) | .66 | 14.34 (2.36) | 14.00 (3.46) | .81 | 14.48 (2.43) | 13.38 (2.00) | .23 |
| Online social support, mean (SD) | | 12.02 (5.07) | 13.57 (4.95) | 10.46 (4.79) | .020 | 11.91 (5.18) | 14.00 (2.00) | .49 | 12.17 (5.23) | 11.13 (4.19) | .60 |
| Offline social support, mean (SD) | | 17.68 (3.52) | 18.71 (1.92) | 16.64 (4.40) | .026 | 17.58 (3.59) | 19.33 (1.15) | .41 | 17.69 (3.64) | 17.63 (2.88) | .96 |
| PNGE-42 (SD) | | 25.95 (21.19) | 45.93 (6.97) | 5.96 (6.14) | <.001 | 27.02 (21.23) | 7.00 (7.55) | .11 | 29.17 (21.07) | 6.63 (6.89) | .004 |
| IGDS-SF9, mean (SD) | | 19.82 (7.57) | 17.82 (4.30) | 21.82 (9.48) | .047 | 18.85 (6.52) | 37.00 (1.00) | <.001 | 17.56 (5.32) | 33.38 (3.85) | <.001 |

[a]For PNGE-High vs. PNGE-Low. For all group tests, *P*-values are from Pearson's chi-squared (categorical variables) and ANOVA (continuous variables).
[b]For IGDS-SF9 <36 vs. ≥36.
[c]For IGDS-SF9 <28 vs. ≥28.

**TABLE 2** Difference in CTRA (adversity) gene expression as a function of covariates, more psychosocially healthy gaming (PNGE-42 ≥37), hedonic well-being, hours/day gaming, and online and offline social support

| | Model 1: Covariates | Model 2: Covariates + PNGE-42 | Model 3: Model 2 + Hedonia | Model 4: Model 2 + Hours/Day | Model 5: Model 2 + Online SS | Model 6: Model 2 + Offline SS |
|---|---|---|---|---|---|---|
| Male = 1 | 0.0510[a] | 0.0546 | 0.0480 | 0.0635 | 0.0528 | 0.0709 |
| | (0.0381) | (0.0355) | (0.0379) | (0.0452) | (0.0363) | (0.0376) |
| | [0.19] | [0.13] | [0.21] | [0.17] | [0.15] | [0.065] |
| BMI | −0.0005 | −0.0002 | −0.0004 | 0.0000 | −0.0006 | 0.0005 |
| | (0.0044) | (0.0038) | (0.0038) | (0.0041) | (0.0039) | (0.0041) |
| | [0.91] | [0.97] | [0.92] | [1.00] | [0.87] | [0.89] |
| Heavy Alcohol = 1 | −0.0742 | −0.0558 | −0.0445 | −0.0646 | −0.0521 | −0.0546 |
| | (0.0780) | (0.0664) | (0.0732) | (0.0717) | (0.0733) | (0.0631) |
| | [0.35] | [0.40] | [0.55] | [0.37] | [0.48] | [0.39] |
| PNGE-High Group = 1 | | −0.0707 | −0.0688 | −0.0669 | −0.0758 | −0.0532 |
| | | (0.0336) | (0.0336) | (0.0347) | (0.0372) | (0.0338) |
| | | [0.040] | [0.046] | [0.059] | [0.047] | [0.12] |
| Hedonia | | | −0.0183 | | | |
| | | | (0.0186) | | | |
| | | | [0.33] | | | |
| Hours/day game | | | | −0.0061 | | |
| | | | | (0.0123) | | |
| | | | | [0.62] | | |
| Online Social Support | | | | | 0.0082 | |
| | | | | | (0.0179) | |
| | | | | | [0.65] | |
| Offline Social Support | | | | | | −0.0318 |
| | | | | | | (0.0183) |
| | | | | | | [0.088] |
| Intercept | −2.2249 | −2.2012 | −2.1934 | −2.1943 | −2.1867 | −2.2384 |
| | (0.1129) | (0.1008) | (0.1026) | (0.1057) | (0.0982) | (0.1048) |
| | [0.00] | [0.00] | [0.00] | [0.00] | [0.00] | [0.00] |
| *N* | 56 | 56 | 56 | 56 | 56 | 56 |

[a]Cell entries represent effect sizes for the resulting linear model coefficients, with standard errors in parentheses and p-values in brackets. Gene expression values were quantile-normalized and log2-transformed, and used as response variables in linear model analyses quantifying the associations of gene expression with key predictor variables.

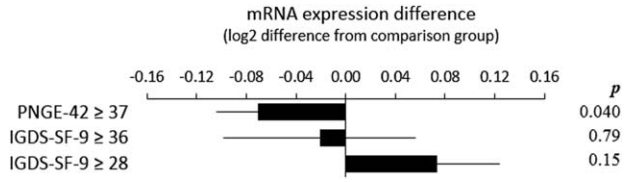


**FIGURE 1** Comparison of CTRA (adversity) gene expression differences, between healthy/disordered gamers and their comparison groups. The first row shows CTRA results for the more highly positive PNGE-42 group compared to the less highly positive experiences group. Persons above and below cut-points on the IGDS-SF9 appear in the next two rows

interviews. Besides identifying a larger group for comparison, this score also corresponded to a natural break in our data (no respondents had IGDS-SF9 sum scores of 26 and 27). Note that all three group pairs (PNGE-High/Low, IGDS-SF9 $< 36/\geq 36$, IGDS-SF9 $< 28/\geq 28$) are reasonably similar in study location, gender, alcohol consumption, age, and self-reported hedonic well-being, with none of those indicators varying in a statistically significant manner across our comparison groups. As expected, some indications of group differences exist, e.g., on mean hours spent gaming per day and on online and offline social support.

Of primary interest in this study are differences in expression of the 50 CTRA indicator genes. Linear model analyses of an a priori-defined CTRA contrast score (weighting 18 pro-inflammatory genes +1 and 32 interferon- and antibody-related genes −1) showed that, controlling for gender, BMI, and heavy alcohol consumption, our ethnographically-based measure of psychosocially proportional gaming, the PNGE-42, was associated with significantly reduced CTRA, thus confirming H1. Details of this result appear in Table 2, first reporting relationships between control variables (gender, BMI, heavy alcohol consumption) and CTRA (Model 1), and then adding PNGE-42 (Model 2), treated as a dichotomized variable contrasting High- and Low-PNGE groups. (Although PNGE-42 is a continuous variable, the separation in scores between the high and low groups is large enough—scores of $\geq 37$ vs $\leq 14$—so that no overall continuum of data points occurs between them.) In the linear model analyses, to limit the number of covariates, we excluded location, age, and other indicators, as they were not significantly correlated to either of our two key predictor scales (PNGE-42 and IGDS-SF9) or to CTRA.

By contrast, the same linear model analyses showed that the IGDS-SF9 $\geq 36$ group (i.e., persons showing "disordered" gaming), contrary to our hypothesis, actually had slightly *lower* CTRA (adversity) scores than the nondisordered group (IGDS-SF9 $< 36$), but the magnitude of these differences did not differ significantly from zero ($b = -0.0211$, $P = .79$; see Figure 1) (disconfirming H2). The IGDS-SF9 $\geq 28$ disordered group *did* differ from the less disordered group (IGDS-SF9 $< 28$) in the expected direction, i.e., having more of the characteristic activated CTRA profile, though again these differences were not statistically significant ($b = 0.0737$, $P = .15$; Figure 1). Finally, when IGDS-SF9 scores were treated as a continuous predictor, they also were unrelated to the 50-gene CTRA indicator score ($b = 0.0037$, $P = .85$).

As shown in Figure 2, ancillary Transcript Origin Analysis comparing the High/Low PNGE-42 groups further indicated that the gene transcripts down-regulated in the more psychosocially positive experience group derived predominately from monocytes in general ($b = 1.79$, $P < .01$ see Figure 2A), and from the proinflammatory/immature CD16- subset of "classical" monocytes in particular ($b = 0.8665$, $P < .01$; Figure 2B). Genes up-regulated in association with balanced gaming experiences derived predominately from the more repair-oriented and mature CD16+ "nonclassical" monocytes ($b = 0.2184$, $P = .0496$; again, Figure 2B). Both patterns are consistent with previous literature on CTRA (Cole, Capitanio, et al., 2015; Powell et al., 2013).

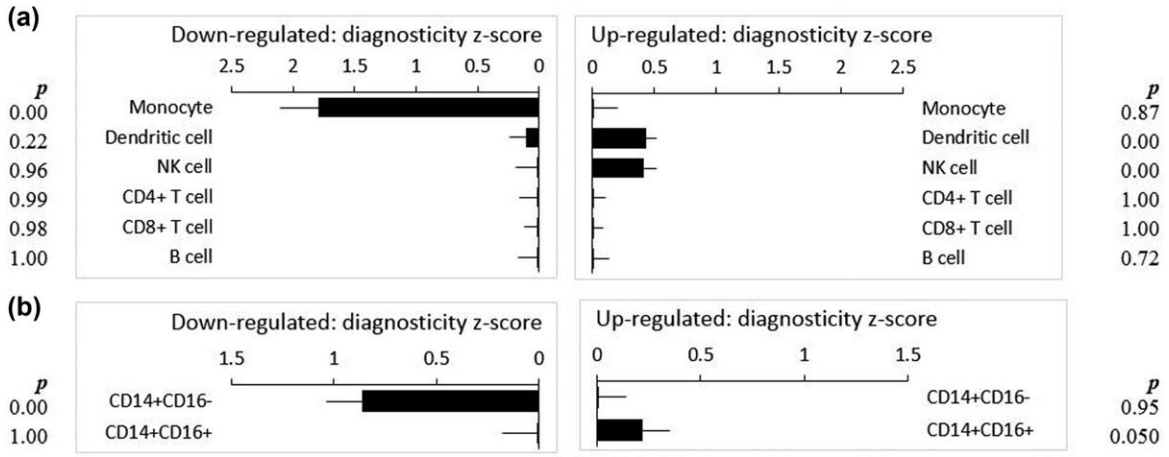


**FIGURE 2** Bioinformatically inferred cellular origins of up-or down-regulated RNA transcripts in the CTRA (adversity) gene expression profile of more/less psychosocially healthy gaming (High vs. Low PNGE Groups)

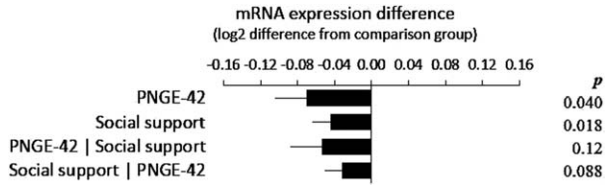


**FIGURE 3** Difference in CTRA (adversity) gener expression as a function of more psychosocially healthy gaming (PNGE-42 $\geq$ 37) and greater offline social support, with associated *P*-values. Bars represent strength of association between indicated predictor variables and the 50-gene CTRA indicator. All estimates use controls for gender, BMI, and heavy alcohol assumption. The first two rows show these relationships without controlling for the other key predictor, while the second two rows show each one controlling for the other. Gene expression values were quantile-normalised and log2-transformed

Finally, to better understand underlying associations between PNGE-42 and CTRA, we examined how the inclusion of a measure of hedonic well-being (a scale sum of three items assessing self-reported happiness, interest in life, and life satisfaction), gaming duration (hours/day), and online and offline social support might change these indicators' relationship. Including hedonic well-being as a predictor of CTRA did not substantially alter the association of PNGE-42 $\geq$ 37 with CTRA (compare PNGE-42 scores in Models 2 and 3 in Table 2). However, controlling for hours played per day did reduce somewhat the relationship between the PNGE-42 and CTRA (Table 2, Model 2 compared to 4). Further, adding *online* social support did not substantially change relationships between proportional gaming experience as measured by PNGE-42 and CTRA (Table 2, Models 2 and 5). By contrast, however, including *offline* social support did substantially weaken that relationship (Table 2, Models 2 and 6). This suggests that proportional gaming experience's association with CTRA involves offline social support as a mutual correlate, as we anticipated in H3.

In Figure 3, we graphically present results showing the relationships among offline social support, proportional gaming, and CTRA. These show that including both PNGE-42 $\geq$ 37 and Offline Social Support in the same model reduces both of those indicators' associations with CTRA. PNGE-42 $\geq$ 37 moves from an effect of $b = -0.0707$ ($P = .040$) to $b = -0.0532$ ($P = .12$), and Offline Social Support drops from $b = -0.0448$ ($P = .018$) to $b = -0.032$ ($P = .088$).

## 4 | DISCUSSION

Our results show that persons with more frequent positive compared to negative internet gaming-related experiences (i.e., higher PNGE-42 scores) are less likely to manifest the elevated CTRA genomic profile; inversely, gamers with fewer positive compared to negative gaming experiences (lower PNGE-42 scores) tend to have an elevated CTRA program. As predicted, our ethnographically-derived measure of the predominance of positive over negative gaming experiences (PNGE-42) was negatively related with elevated CTRA gene expression (H1), as well as with mechanistically related alterations in monocyte subset activation. Further, associations between our key PNGE-42 indicator and CTRA held even when controlling for a measure of hedonic well-being, suggesting that the association of internet play patterns with CTRA reflected something beyond pre-existing subjective well-being as a possible cause of both of them (Ferguson et al., 2011; Kardefelt-Winther, 2014a; Mentzoni et al., 2011; Snodgrass, Lacy, et al., 2014). These findings advance understandings of the psychobiology of play (Panksepp, 2004, 2007, 2010; Pellis & Pellis, 2007), confirming via transcriptome methods how certain forms of internet play can be associated with biological manifestations of chronic threat, uncertainty, and distress (Cole, 2017; Cole, 2014), a topic of current human biological interest (Montag, Sindermann, Becker, & Panksepp, 2016). Overall, our study shows the greater distress some gamers experience compared to others is real and embodied (i.e., at the molecular level in RNA patterns) rather than simply reflecting societal moral panic and crisis (Golub & Lingley, 2008; Szablewicz, 2010).

Moreover, PNGE-42's predictive power stemmed from its detection of distinctive behavioral patterns like hours played per day (Baggio et al., 2016; Charlton & Danforth, 2010; Demetrovics & Király, 2016; Griffiths, 2010; James & Tunney, 2017), and social processes such as loneliness (Kim et al., 2009; Nowland et al., 2018; Schiano et al., 2014; Snodgrass et al., 2018), which reveal internet gaming's broader place within a player's life. Regarding the social processes, our study demonstrates that a significant portion of PNGE-42 scores' association with CTRA gene expression is shared with *offline* (but not *online*) social support (H3). In our study, offline social support outweighs its online counterpart in its relationship to more positive genomic profiles, echoing concerns about the potential negative health impacts when, for certain players, life online competes with and even partially replaces social relationships located primarily offline (Putnam, 2000; Snodgrass, Lacy, Dengah, & Fagan, 2011; Turkle, 2012). That said, it is important to note that the health implications of the observed molecular differences remain to be verified in future research. The CTRA shows a manifestation of disordered gaming in molecular physiology, but this biology serves at best as a precondition for the development of disease and should not be taken as a direct indicator of somatic illness per se.

Based on prior functional genomics research pointing to the way loneliness in particular influences CTRA expression (Cacioppo et al., 2015; Cole, Capitanio, et al., 2015; Cole, Levine, et al., 2015), one likely explanation for these results is that underlying difficulties in social support shape both

problematic gaming experience and CTRA. From this perspective, problem gaming would be a manifestation of broader patterns of biopsychosocial stress and distress, rather than being source of such stress *sui generis*. In medical anthropological terms, problem gaming appears likely to be a salient idiom for experiencing, communicating, and even attempting to resolve distress among emerging adults (Nichter, 1981, 2010). That is, so-called "internet gaming disorder" (IGD) represents to a large extent a rather familiar response to psychosocial problems such as loneliness, whose health effects are well established, rather than a new psychiatric disorder *per se*. Of course, deficiencies in social support might operate here as a proxy for even broader patterns of psychosocial dysfunction that produce CTRA, although this interpretation is mitigated somewhat by our finding that the association of PNGE-42 with CTRA was not substantially affected by controlling for hedonic well-being, which is a more direct measure of such underlying distress and dysfunction. Whatever the pattern of causation, however, our findings do show that psychological distress related to internet gaming has real biological correlates, an important advance for human biological and medical anthropological studies of wellness and distress in these online contexts (Kuss, Griffiths, & Pontes, 2017; Montag et al., 2016; Pontes, Kuss, & Griffiths, 2017). Nonetheless, as in the experience of many persons who abuse substances (alcohol, opiates, tobacco, etc.), regarding problematic internet play as originating in pre-existing and broader pattern of dysfunction does not preclude it becoming an independent and self-sustaining source of further stress and distress (Kreek et al., 2005; Pohorecky, 1991; Sinha, 2008).

Finally, another important finding here was that the current field-standard measure of internet gaming disorder (IGDS-SF9) was not associated with CTRA genomic distress in our sample using the currently suggested cut-point of 36 (Pontes & Griffiths, 2015) (again, disconfirming H2). Neither did we find such an association using our ethnographically-supported 28 cut-point on that scale, nor when treating IGDS-SF9 as a continuous variable. This may reflect the ineffectiveness of this measure, modeled on substance abuse instruments, to adequately capture the experience of problematic gaming. However, this nonassociation could also be a sample artifact related to the small number of IGD $\geq$ 36 classified gamers in our study sample. Nevertheless, we would note that comparisons of groups with similarly small numbers has detected meaningful differences in other gene expression research (Cole, 2017; Cole et al., 2007; Cole, 2014). In any case, a genomics-based critical evaluation of IGD as a concept, and thus of current APA and WHO proposals related to problem gaming, would be best served by a sample including substantial numbers of gamers crossing clinical IGD thresholds, appropriately matched to nondisordered controls. Further, such future studies should keep in mind the potential limits of rigid diagnostic thresholds and thus strict clinical cut-points to effectively distinguish human biological differences of the kinds described in our study, compared to the top and bottom quartiles approach we took, which more effectively separated the more from the less distressed gamers. Whatever the path of future research, overall, the biocultural methods and perspectives sketched in our work can help inform not only neurobiological understandings of play, but also APA, WHO, and medical anthropological debates about human wellness and suffering in both technologically-mediated and other novel cultural contexts.

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## CONFLICT OF INTERESTS

The authors declare no conflict of interest.

## AUTHOR CONTRIBUTIONS

J.G.S., H.J.F.D., M.G.L., and S.W.C designed research; J. G.S., H.J.F.D., M.G.L., R.E., E.P., J.M.G.A., and S.W.C. performed research; S.W.C. contributed new reagents/analytic tools; J.G.S., H.J.F.D., M.G.L., R.E., E.P., and S.W.C analyzed data; and J.G.S., H.J.F.D., M.G.L., and S.W.C wrote the paper.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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