Affective reactivity to daily stressors and immune cell gene expression in the MIDUS study

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ABSTRACT

Affective reactivity to stress is a person-level measurement of how well an individual copes with daily stressors. A common method of measuring affective reactivity entails the estimation of within-person differences of either positive or negative affect on days with and without stressors present. Individuals more reactive to common stressors, as evidenced by affective reactivity measurements, have been shown to have increased levels of circulating pro-inflammatory markers. While affective reactivity has previously been associated with inflammatory markers, the upstream mechanistic links underlying these associations are unknown. Using data from the Midlife in the United States (MIDUS) Refresher study (N = 195; 52% female; 84% white), we quantified daily stress processes over 10 days and determined individuals' positive and negative affective reactivities to stressors. We then examined affective reactivity association with peripheral blood mononuclear cell (PBMC) gene expression of the immune-related conserved transcriptional response to adversity. Results indicated that individuals with a greater decrease in positive affect to daily stressors exhibited heightened PBMC *JUNB* expression after Bonferroni corrections (*p-adjusted* < 0.05). *JUNB* encodes a protein that acts as a transcription factor which regulates many aspects of the immune response, including inflammation and cell proliferation. Due to its critical role in the activation of macrophages and maintenance of CD4+ T-cells during inflammation, *JUNB* may serve as a potential upstream mechanistic target for future studies of the connection between affective reactivity and inflammatory processes. Overall, our findings provide evidence that affective reactivity to stress is associated with levels of immune cell gene expression.

1. Introduction

Stress is a ubiquitous experience. At global and daily levels, and across various contexts, stress can contribute to adverse psychological and physiological health outcomes for individuals (Almeida et al., 2009; Charles et al., 2013; McGonagle and Kessler, 1990; Surachman et al., 2019). In recent decades, there has been increasing work examining the mechanisms by which stress can 'get under the skin' to impact physical and biological health (Epel et al., 2018; Wright et al., 1998). Chronic and acute stress have been shown to contribute to general 'wear and tear' on the brain and body, exacerbating chronic conditions, increasing allostatic load, and leading to dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, which may result in lasting health impacts through dysregulated inflammatory pathways (Kiecolt-Glaser and Glaser, 1999; Logan and Barksdale, 2008; McEwen, 1998; Ong et al., 2017; Piazza et al., 2010).

1.1. Daily stress, affective reactivity, and health

Stress can affect health and well-being by disrupting the everyday lives of individuals. Stress research has largely focused on major or chronic stressors such as divorce or unemployment (Minnotte and Yucel, 2018; Pearlin et al., 1981; Wilkinson, 2016). In contrast to major stressors, daily stressors are usually more minor and short-lived and yet can be frequent and strong enough to create strains in daily life (Almeida, 2005; Piazza et al., 2013). Examples of daily stressors include interpersonal conflicts, work deadlines, and providing care for others (Almeida, 2005). These naturally-occurring stressors evoke emotional and behavioral responses that can have acute and prolonged impacts on health. Frequent exposure to daily stressors has a detrimental immediate effect on emotional (Stawski et al., 2008), physiological (Stawski et al., 2013), and cognitive (Sliwinski et al., 2006) well-being, and an accumulated effect on physical (Piazza et al., 2013) and mental health outcomes (Charles et al., 2013). Indeed, the daily lives of midlife and older adults in the United States have changed in past decades such that these daily stressors are becoming more common; this has long-lasting implications for health and well-being. According to Almeida et al. (2020), "adults in the 2010s report experiencing stressors on 2% more days than in the 1990s, which translates to an additional week of stressors across a year" (p. 511).

Previous stress research has also shown that the occurrence of daily stressors is distinguishable from how individuals emotionally react to stressors. Stressor exposure is often operationalized as the frequency of stressors reported, whereas affective reactivity to daily stressors is often assessed as the difference in negative or positive affect on stressor days versus non-stressor days (Almeida et al., 2022). Affective reactivity to daily stressors, is a person-level measure of how well an individual copes with stressors (Gunaydin et al., 2016; Piazza et al., 2013; Sin et al., 2020). Affective reactivity to daily stress has been shown to be associated with multiple negative health outcomes. For example, while daily stressors are associated with daily negative affect, individuals who have higher affective reactivity to daily stress also exhibit chronic affective disorders (i.e., major depressive disorder or generalized anxiety disorder) (Charles et al., 2016; Charles et al., 2013; Charles et al., 2009). Additionally, using data from the Midlife in the United States (MIDUS) National Study of Daily Experiences (NSDE), it was found that participants with higher affective reactivity to daily stressors at the initial wave (NSDE I; 1996–1997) had an increased likelihood of reporting a chronic physical health condition 10 years later (Piazza et al., 2013). Another study utilizing MIDUS data found that there was a significant association between number of daily stressors as well as higher negative affective reactivity in NSDE I and risk of mortality 20 years later.

1.2. Daily stress, affective reactivity, and inflammation

In addition to mental and physical health conditions, increased affective reactivity to daily stressors has been shown to be associated with multiple common markers of inflammation. Inflammation is an important biological process by which the immune system defends the body from foreign organisms. However, excessive levels inflammation or low-grade chronic inflammation is involved in the development of chronic conditions such as cardiovascular and autoimmune diseases (Danesh et al., 2004). Previous research has shown that individuals who encountered more frequent daily stressors had higher levels of circulating inflammatory markers such as interleukin-6 (IL-6) and C-reactive protein (CRP) than those with less frequent stressors (Fuligni et al., 2009; Gouin et al., 2012). Conversely, frequency of daily positive events has been shown to be associated with lower IL-6, CRP, and fibrinogen levels in aging adults (Sin et al., 2015a). Though limited, studies have found that affective reactivity to daily stressors are associated with elevated inflammation in adolescence (Chiang et al., 2015; Chiang et al., 2019b) and adulthood (Sin et al., 2015b). A study using MIDUS II (2004–2006) data found that individuals who experienced a greater decrease in positive affect or greater increase in negative affect on stressor days versus non-stressor days had elevated levels of inflammatory markers, such as IL-6 and CRP (Sin et al., 2015a; Sin et al., 2015b). Together, affective reactivity to daily stressors may contribute to heightened inflammation and subsequent poor health outcomes.

1.3. Stress and gene expression

Although past research has revealed significant associations between affective reactivity and inflammation, less is known about the underlying biological mechanisms of these associations. One possible linkage between affective reactivity and inflammation is individual differences in expression levels of genes that encode the proteins that mediate immune-related responses (e.g., inflammatory cytokines, antimicrobial molecules, etc.). Increases in molecular markers of inflammation are accompanied and preceded by changes in more fundamental biological processes. Because most markers of inflammation are various types of proteins (TNF-a, IL-6, CRP, etc.), it follows that increases in these markers may also be accompanied by increases in levels of gene expression that regulate inflammatory processes.

Previous work has documented a connection between early and later-life adversity and changes in transcriptional profiles of genes that are important in the inflammation and antiviral processes (Cole et al., 2012; Cuevas et al., 2022; Friedman et al., 2015; Holmes et al., 2019; Jiang et al., 2019; Lopez et al., 2021; Walker et al., 2014). This phenomenon, known as the 'conserved transcriptional response to adversity' (CTRA), provides an ideal list of candidates for detecting gene expression changes underlying associations between affective reactivity and negative health outcomes. The CTRA captures a pattern of immune-related gene expression that includes an up-regulation of genes involved in inflammation and a down-regulation of genes involved in type-1 interferon response and antibody production (Cole, 2013, 2019).

Behavioral immune response theory and CTRA-related work (Cole, 2013; Powell et al., 2013) suggests that similar to physical injuries, subjective distress and psychological impairment result in over-activation of pro-inflammatory genes as the immune system recognizes these stimulations as threats to the body. Chronic stress caused by social adversity has been shown to activate CTRA (Cole et al., 2015); and social disruption and isolation caused by the COVID-19 pandemic could similarly contribute to chronic CTRA activation, potentially increasing susceptibility to viral infections due to suppression of anti-viral gene expression (Cole et al., 2021; Mattos dos Santos, 2020). In contrast, positive psychological well-being is inversely associated with CTRA activation (Fredrickson et al., 2015). There have been relatively few studies thus far that examine how daily stress processes may contribute to gene expression, outside of animal models (Allen et al., 2010). However, recent work has found that daily interpersonal stress was associated with greater expression of inflammation-related genes during late adolescence (Chiang et al., 2019a; Chiang et al., 2019b); and a study using MIDUS Refresher data found significant associations between daily discrimination and inflammatory gene expression, particularly for racially minoritized males (Cuevas et al., 2022). Overall, however, particularly in the context of adulthood, there is still a significant dearth of literature examining the associations between daily stress and gene expression—and as far as we know, there have been no studies that examine how affective reactivity to daily stressors may impact gene expression. A notable exception is a recent study reporting associations between immune gene expression and emotion, however, this study does not address stress or affective reactivity (Rahal et al., 2023). Expression of the inflammatory and antiviral genes involved in CTRA may provide a possible mechanism by which individuals' affective reactivity to daily stressors biologically impact inflammation and subsequent health outcomes.

1.4. The current study

While many health-related outcomes have been studied in relation to affective reactivity, the specific molecular and cellular mechanisms of increased health risk have not received as much attention. Extending the work by Sin et al. (2015), the current study aimed to examine the association between affective reactivity to daily stressors and expression of immune-related genes among midlife adults by using the CTRA pre-selected set of genes. This study explored how individual differences in affective response to daily stressors are associated with composite and individual expression of these genes. We hypothesized that individuals with higher magnitudes of negative affective reactivity and/or positive affective reactivity to daily stress will have increased activation of CTRA pro-inflammatory genes and decreased expression of CTRA antiviral genes.

2. Materials & methods

2.1. Participants and design

Data for the current analysis were drawn from the MIDUS study Refresher Cohort. The MIDUS study is an ongoing national survey designed to examine the role of behavioral, psychological, and social factors in age-related variation in health and well-being. MIDUS started in 1994–1995, recruiting 7,108 adults aged 25–74. The longitudinal follow-ups were conducted in 2004–2006 (MIDUS 2; N = 5,555) and 2013–2015 (MIDUS 3; N = 3,683). In 2011–2014, an additional sample called the MIDUS Refresher Cohort of 3,577 adults aged 25 to 74 was recruited to replenish the number of middle-aged adults in the original MIDUS cohort. The MIDUS Refresher survey conducted the same assessments as the original MIDUS study, where participants first completed baseline phone interviews and then completed self-administered questionnaires by mail (response rate = 73.0%).

The sample for the current study included individuals from the MIDUS Refresher Cohort who participated in both the Daily Diary (collected 2012–2014) and the Biomarker (collected 2012–2015) sub-projects. A sample of 782 adults were enrolled in the Daily Diary (or NSDE) study and completed daily telephone interviews across eight consecutive evenings. Of these 782 individuals, 234 participated in the Biomarker project which assessed their physical health and physiological functioning. Participants were invited to one of the three regional clinical research units located on the west coast, Midwest, and east coast, and stayed overnight to complete biomarker assessments.

Our analytical sample included only individuals that (1) reported having experienced both days with and without a stressor, (2) consented to the use of their genetic information for analysis, and (3) did not have any missing data on key variables used in the analyses. These exclusions resulted in the final analytic sample of 195 participants with 1,500 diary days (mean age: 48.3; age range 25–75; 52% female; 84% white). A graphical description of our inclusion/exclusion criteria is presented in Supplementary Fig. 1. Our sample was not significantly different from those excluded from the analyses in age (t=−0.52 (780); p=0.700), sex (χ^2(1)=1.16, p=0.282), and race composition (χ^2(1)=0.25, p=0.617).

2.2. Daily measurements and affective reactivity

2.2.1. Daily stressors

Data on participants' daily experiences were obtained during the daily telephone interviews as a part of the Daily Diary subproject. Daily stressors were assessed using the Daily Inventory of Stressful Events (Almeida et al., 2002) which asked whether participants experienced seven types of stressors (argument, avoided an argument, stressor at work or school, stressor at home, discrimination, stressful event that happened to a close friend or family member, and any other stressor) in the past 24 h. A dichotomous variable was created to indicate whether a given day was a stressor-day on which participants experienced at least

one stressor.

2.2.2. Daily affect

Daily positive affect (PA) and negative affect (NA) were measured during daily telephone interviews using scales developed for the MIDUS study (Kessler et al., 2002; Mroczek and Kolarz, 1998). The scale for positive affect included 13 items (felt in good spirits, cheerful, extremely happy, calm and peaceful, satisfied, full of life, close to others, like you belong, enthusiastic, attentive, proud, active, and confident), and negative affect included 14 items (felt restless or fidgety, nervous, worthless, so sad nothing could cheer you up, everything was an effort, hopeless, lonely, afraid, jittery, irritable, ashamed, upset, angry, and frustrated). Participants rated each item on a 5-point scale ranging from 0 (*none of the time*) to 4 (*all of the time*). Daily PA and NA were calculated by averaging items of each scale. Between-person reliability for PA was 0.97 and NA was 0.95, and within-person reliability for PA was 0.87 and NA was 0.81 (Geldhof et al., 2014).

2.3. CTRA gene expression

Blood samples for gene expression analysis were obtained as part of a fasting blood draw completed on the morning of the second day of the MIDUS Biomarkers project visit (2012–2016; see https://www.icpsr. umich.edu/icpsrweb/ICPSR/studies/36901). Whole blood samples were collected using a BD Vacutainer CPT Tube for separation of mononuclear cells from whole blood and were subsequently centrifuged for 20 min at 1800g at room temperature. RNA from peripheral blood mononuclear cell (PBMC) pellets were extracted using the Qiagen Rneasy kit and stored at –70°C.

PBMC gene expression assays in the MIDUS-Refresher biomarker study were conducted in 2017–2018. Extracted RNA samples were tested for suitable RNA yield and RNA integrity number (RIN; 5.91 ± 1.40), and subjected to transcriptome profiling by RNA sequencing. cDNA library preparation was performed using Lexogen's QuantSeq FWD 5′ gene counting assay and was sequenced on an Illumina HiSeq 4000 instrument. cDNA library preparation was carried out in 96-sample batches. Each sample had more than 10 million single-strand 65-nucleotide reads sequenced. Sequenced reads were aligned to the consensus human transcriptome and quantified on a per-gene basis using the STAR aligner. Raw read counts for each gene were normalized to transcript counts per million (CPM) of total mapped reads, log2 transformed and subjected to a standard endpoint quality control screen to exclude aberrant data (r < 0.85 correlation of sample-specific transcriptome profile with other profiles).

A total of 59 specific transcripts were extracted from this whole-transcriptome data, 51 of which were part of the CTRA gene list and the remaining 8 were used as surrogate markers to control for proportions of immune cell subtypes. The CTRA genes were comprised of two subcategories: 19 pro-inflammatory genes (*CXCL8, FOS, FOSB, FOSL1, FOSL2, IL1A, IL1B, IL6, JUN, JUNB, JUND, NFKB1, NFKB2, PTGS1, PTGS2, REL, RELA, RELB,* and *TNF*) and 32 antiviral genes (*GBP1, IFI16, IFI27, IFI27L1, IFI27L2, IFI30, IFI35, IFI44, IFI44L, IFI6, IFIH1, IFIT1, IFIT2, IFIT3, IFIT5, IFITM1, IFITM2, IFITM3, IFITM4P, IFITM5, IFNB1, IGLL1, IRF2, IRF7, IRF8, JCHAIN, MX1, MX2, OAS1, OAS2, OAS3,* and *OASL*). Genes used to account for varying proportions of immune cell subtypes were *CD3E, CD3D, CD4, CD8A, CD14, CD19, FCGR3A,* and *NCAM1*. CTRA genes with low counts (average expression level < 0.5 log2 CPM reads) were excluded from all analyses (*CXCL8, IL1A, FOSL1, IL6, IFI27, IFITM4P, IFITM5, IFNB1,* and *IGLL1*), leaving 15 pro-inflammatory and 27 antiviral genes.

CTRA subscores were created by averaging log2 CPM gene expression values that were mean-centered within-gene (i.e., log2 CPM expression values for each gene were subtracted from the mean expression value for that gene) across each subscore category (pro-inflammatory and antiviral). The difference between the pro-inflammatory and antiviral composite scores was also calculated to

create a combined overall CTRA score. The pro-inflammatory, antiviral and overall CTRA composite scores were then sample mean-centered.

2.4. Covariates

At the within-person level, weekend (vs. weekday) was included as a covariate when examining the association between daily stressor and daily affect. At the between-person level, age, sex, race, and household income variables were included as covariates. During visits, participants provided information about their physical health and health behaviors. The total number of chronic conditions diagnosed by physician (e.g., asthma, tuberculosis, diabetes, heart disease, neurological disorders) and body mass index (BMI; kg/m2) were included as covariates to adjust for their physical health. Smoking status (whether they smoked cigarettes regularly) and a history of alcohol consumption during the past month (number of drinks/week) were included as health behavior covariates. In addition, assay plate batch, RIN and the prevalence of transcripts marking T lymphocytes subsets (*CD3D, CD3E, CD4, CD8A*), B lymphocytes (*CD19*), NK cells (*CD16/FCGR3A, CD56/NCAM1*), and monocytes (*CD14*) were included as technical covariates. Lastly, a time interval between the two assessments (Daily Diary and Biomarker) was included as a covariate.

2.5. Statistical analysis

This study utilized multilevel structural equation modeling (MSEM) to examine the association between PA and NA reactivity to daily stressors and gene expression. MSEM merges features of multilevel modeling – which handles hierarchically structured data – and structural equation modeling, allowing a multivariate examination of variables across different levels of analysis (Asparouhov et al., 2018; Rush et al., 2019). In MSEM, the random effects drawn at each level can be simultaneously included in higher level models. This flexibility allowed the current examination, where individual differences in within-person association between daily stressor and affect (affective reactivity) were simultaneously modeled at the within-person level, and were also used as predictors of CTRA gene expression scores at the between-person level. All effects were estimated simultaneously in Mplus Version 8 using Bayesian estimation.

A conceptual model is presented in Fig. 1. The within-person level of the models examined the daily association between stressor and affect, where the occurrence of daily stressor was included as a predictor of daily affect on a given day. Estimated random slopes (i.e., daily within-person association between stressor and affect) represent individuals' affective reactivity to daily stressors. The between-person level of the models tested whether individual differences in affective reactivity to daily stressors were associated with gene expression by including latent random slopes as predictors of gene expression. Continuous variables included as covariates at the between-person level were centered at the grand mean. Multiple iterations of statistical models with a varying number of covariates were performed to ensure no associations were missed due to covariate confounding (see Supplementary Table S1, all p-values reported therein are unadjusted). All models returned similar results and the model containing all covariates was used in our final results (see Supplementary Table S1: Full Model – v4). Sensitivity analysis also examined the impact of depression and anti-inflammatory medications. 68 individuals (34.87%) self-reported having ever been diagnosed with depression and 93 individuals (47.69%) self-reported ever taking anti-inflammatory medications. Results remained unchanged when including both depression and anti-inflammatory medication covariates (see Supplementary Table S1: Full Model – v6). A total of 90 models were tested (45 PA reactivity models [3 composite and 42 individual] and 45NA reactivity models [3 composite and 42 individual]); therefore, a Bonferroni-adjusted p-value threshold ($p=0.0005$) was used to determine significance in order to reduce type-1 error rate due to multiple hypothesis testing.

3. Results

3.1. Demographic characteristics

Demographic characteristics of our final sample (N=195) are provided in Table 1. The majority of participants were white (83.59%) and had a relatively high household income ($94,051 ± $65,518). Participants had an above average BMI (29.90 ± 7.76) and had an average of 4 chronic health conditions. In addition, 16 individuals (8.21%) reported
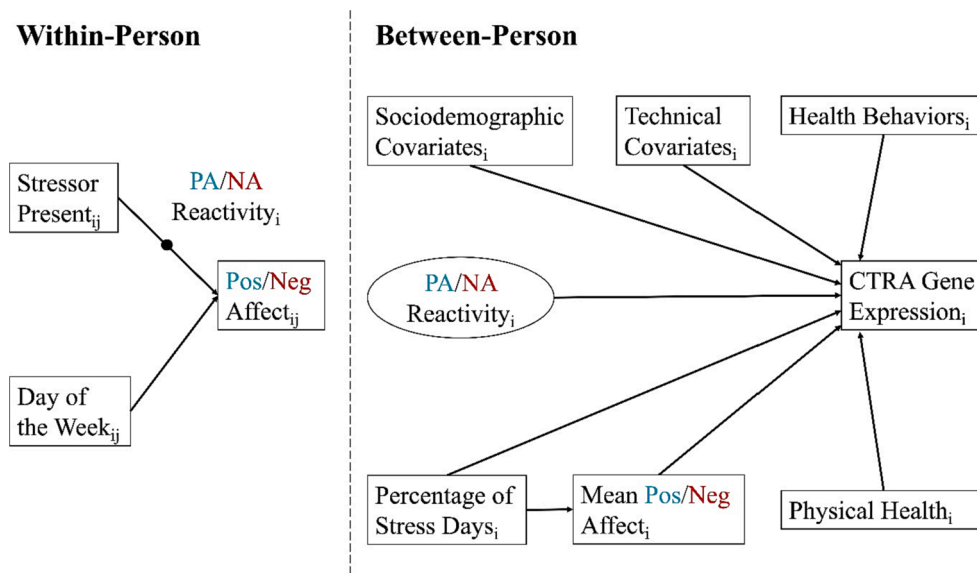

Fig. 1. Multilevel Structural Equation Models.
A representation of the MSEMs used to model the associations of PA and NA reactivity with CTRA gene expression measurements. At the within-person level (left), the occurrence of a stressor was used to predict daily PA/NA. PA and NA reactivity were modeled as the random slope representing an individual's change in affect on stressor days vs. non-stressor days. At the between-person level (right), PA and NA reactivity were used to predict individual CTRA gene expression measurements (composite or individual gene scores). A total of 90 models were constructed (45 PA and 45 NA).

Table 1
Sample descriptive statistics.

Participant Characteristics (N = 195)	Mean (SD) or N (%)
Sociodemographic Variables	
Female	102 (52.31%)
Age, years	48.32 (11.70)
White Race	163 (83.59%)
Household Income	$94,051 ($65,518)
Daily Stress and Affect	
Stressor Frequency (% stressor days)	45.5% (21.5%)
Weekend, days	407 (27.1%)
Average PA	2.46 (0.86)
Average NA	0.13 (0.06)
PA Reactivity	−0.11 (0.03)
NA Reactivity	0.13 (0.06)
Physical Health	
BMI	29.90 (7.76)
Number of Chronic Conditions	3.98 (3.18)
Health Behaviors	
Smoking, yes	16 (8.21%)
Days per Week of Alcohol Consumption	1.44 (1.35)

PA and NA reactivity were estimated for descriptive purposes using multilevel modeling where PA and NA were predicted by the occurrence of daily stressor. PA and NA reactivity are defined by random slopes representing individuals' change in affect on stressor days vs. non-stressor days. Higher values for PA reactivity indicate smaller decreases in PA on stressor days compared with non-stressor days. Higher values of NA reactivity indicate greater increases in NA on stressor days compared with non-stressor days.

having a habit of smoking and participants consumed alcohol one day per week, on average.

Our overall sample exhibited a survey compliance rate of 96.15%

amounting to a total of 1,500 individual days of information collected. 407 days (27.1%) of recorded information took place on weekends. Each individual experienced a stressful event on around half of the days they reported daily diary information (average of 45.5% ± 21.5% stressor days per person).

3.2. Affective reactivity and composite CTRA scores

We first tested whether PA and NA reactivity were associated with the CTRA pro-inflammatory subscore, the CTRA antiviral subscore and the CTRA overall composite score. Neither PA reactivity nor NA reactivity were significantly associated with any CTRA composite scores (Table 2). Additionally, no sociodemographic, physical health, or health behavior covariates were significantly associated with any CTRA composite scores ($p>0.05$).

3.3. Affective reactivity and individual CTRA gene expression

Following CTRA composite scores, we next tested whether PA and NA reactivity were associated with individual CTRA gene expression values. After correcting for multiple testing, we observed one gene in the pro-inflammatory set – *JUNB* – that was significantly associated with PA reactivity (β=-1.737; *p-adjusted*<0.05). *JUNB* had a negative association with PA reactivity scores, indicating that individuals with a greater decrease in PA in response to stress had higher *JUNB* expression values. Additionally, although not significant after correcting for multiple hypothesis testing, the expression of the following genes were nominally associated with PA reactivity: *TNF* (β=4.799; *p-unadjusted*=0.05), *IRF8* (β=-2.331; *p-unadjusted*=0.01), *JCHAIN* (β=-3.419; *p-unadjusted*=0.03),

Table 2
CTRA Composite Score Model Results.

	Positive Affective Reactivity			Negative Affective Reactivity		
	Pro-inflammatory	Antiviral	Overall CTRA	Pro-inflammatory	Antiviral	Overall CTRA
Daily Stress and Affect						
Stressor Frequency (% stressor days)	−0.024	−0.006	−0.005	−0.036	0.034	−0.047
Average Affect	0.015	−0.056	0.071	0.013	0.023	−0.041
Affective Reactivity	−0.267	−0.376	0.226	0.186	0.490	−0.210
Sociodemographic Variables						
Sex	−0.002	−0.002	0.001	−0.001	−0.006	0.005
Age	0.000	0.003	−0.003	0.001	0.002	−0.003
Household Income	−0.009	−0.020	0.013	−0.007	−0.018	0.012
Race	−0.005	0.027	−0.040	0.001	0.015	−0.004
Physical Health						
BMI	−0.016	−0.018	−0.002	−0.037	−0.018	−0.033
Number of Chronic Conditions	0.007	−0.007	0.014	0.006	−0.005	0.013
Health Behaviors						
Smoking Status	−0.084	−0.016	−0.071	−0.089	−0.010	−0.080
Alcohol Consumption	0.002	0.013	−0.011	0.001	0.011	−0.011
Technical Variables						
Time Between Projects	−0.004	−0.002	−0.002	−0.004	−0.003	−0.003
RIN	−0.014	0.077**	−0.096***	−0.021	0.070**	−0.095***
CD3E	0.004	−0.055	0.054	0.003	−0.071	0.072
CD3D	0.019	−0.002	0.024	0.021	0.006	0.016
CD4	0.074*	0.117*	−0.042	0.073*	0.106*	−0.038
CD8A	−0.003	0.027	−0.026	0.001	0.026	−0.027
CD14	0.181***	0.153	0.029	0.185***	0.165***	0.022
CD19	−0.003	−0.019	0.013	−0.002	−0.016	0.015
FCGR3A	0.046**	0.075**	−0.030	0.048*	0.072*	−0.017
NCAM1	−0.018	−0.031	0.012	−0.017	−0.026	0.006
Batch 2	−0.170	0.001	−0.194	−0.168	−0.015	−0.160
Batch 3	−0.007	0.457**	−0.448**	0.011	0.465**	−0.435***
Batch 4	−0.048	0.312*	−0.349*	−0.024	0.333*	−0.338*
Batch 5	0.159	0.508**	−0.325	0.159	0.532**	−0.337
Batch 6	−0.039	0.481*	−0.526*	−0.029	0.498*	−0.505*
Batch 7	−0.001	0.144	−0.129	0.012	0.162	−0.079
Batch 8	0.387**	0.541**	−0.143	0.393**	0.575*	−0.123

MSEM estimates of PA and NA reactivity models for all CTRA composite scores. Average affect and affective reactivity variables for PA reactivity models were all positive affect and for NA reactivity models were all negative affect. No multiple testing corrections were performed with composite score models. * p < 0.05; ** p < 0.01; *** p < 0.001.

and *OAS3* (β=5.153; *p-unadjusted*=0.02; see Supplementary Table S1: Full Model – v4).

No genes exhibited significant associations with NA reactivity after multiple testing corrections, however the following genes were nominally significant: *PTGS2* (β=-2.367; *p-unadjusted*=0.01), *IFI27L2* (β=-2.015; *p-unadjusted*=0.01), and *IRF8* (β=2.605; *p-unadjusted*=0.03; see Supplementary Table S1: Full Model – v4). Estimates for PA and NA reactivity models for all individual genes are shown in Fig. 2.

4. Discussion

We analyzed the associations between daily levels of both PA and NA reactivity and pro-inflammatory and antiviral gene expression, aiming to uncover potential mechanistic links between affective reactivity to stress with immune-related gene expression. Using a predefined set of genes included in the CTRA list, we found that one gene in the pro-inflammatory set, *JUNB,* was associated with PA reactivity after correcting for multiple testing. Specifically, individuals whose PA decreased more in response to stress exhibited heightened *JUNB* expression. *JUNB*, a subunit of the activator protein 1 (AP-1) protein complex, plays an important role in cell transformation, proliferation, differentiation and apoptosis (Ameyar et al., 2003). The AP-1 protein complex exerts its molecular influence as a transcription factor, regulating the expression of a variety of other important genes such as those encoding inflammatory cytokines, antimicrobial molecules, metabolic processes, and cell proliferation (Li et al., 1999). Further, *JUNB* has been shown to play a critical role in the classical and alternative activation of macrophages, modulating the expression of a plethora of inflammatory

markers in these cells (Fontana et al., 2015), as well as maintenance of CD4+ T-cells during inflammation (Carr et al., 2017). Indeed, additional analyses indicated that there are significant correlations between *JUNB* expression and both *CD4* expression (r=0.734, *p*<0.001) and *CD14* expression (r=0.783, *p*<0.001), further strengthening the connection between *JUNB* and macrophage/CD4+ activity. Given that *JUNB* fundamentally mediates immune cell reactivity to external stimuli (e.g., microbes, tissue injury, cytokines, etc.), these data suggest that affective reactivity to psychological stress may potentially be linked to immunologic reactivity to immunologic stimuli. Additionally, although not Bonferroni significant, both *OAS3* and *IFI27L2* showed associations with PA and NA reactivity, respectively, in the directions that we hypothesized.

In contrast, we found no significant associations between CTRA composite scores (i.e., pro-inflammatory, antiviral, or overall CTRA) and PA or NA reactivity. Previous research with the MIDUS Refresher Cohort assessing the associations between CTRA composite scores and Big Five personality traits was also unsuccessful in finding any significant associations (Hobbs et al., 2021). It is possible that the CTRA composite scores are not sensitive enough for capturing subtle changes of individual gene expression profiles in relation to psychological/behavioral traits (Cole, 2019). It is also possible that more informative measurements of pro-inflammatory and antiviral gene regulation could be constructed using more advanced statistical techniques to create different composite scores (Fredrickson et al., 2015; Kitayama et al., 2016; Kohrt et al., 2016; Nelson-Coffey et al., 2017) instead of averaging expression scores across genes, and that these more nuanced measurements of CTRA gene expression would be associated with PA and NA reactivity.
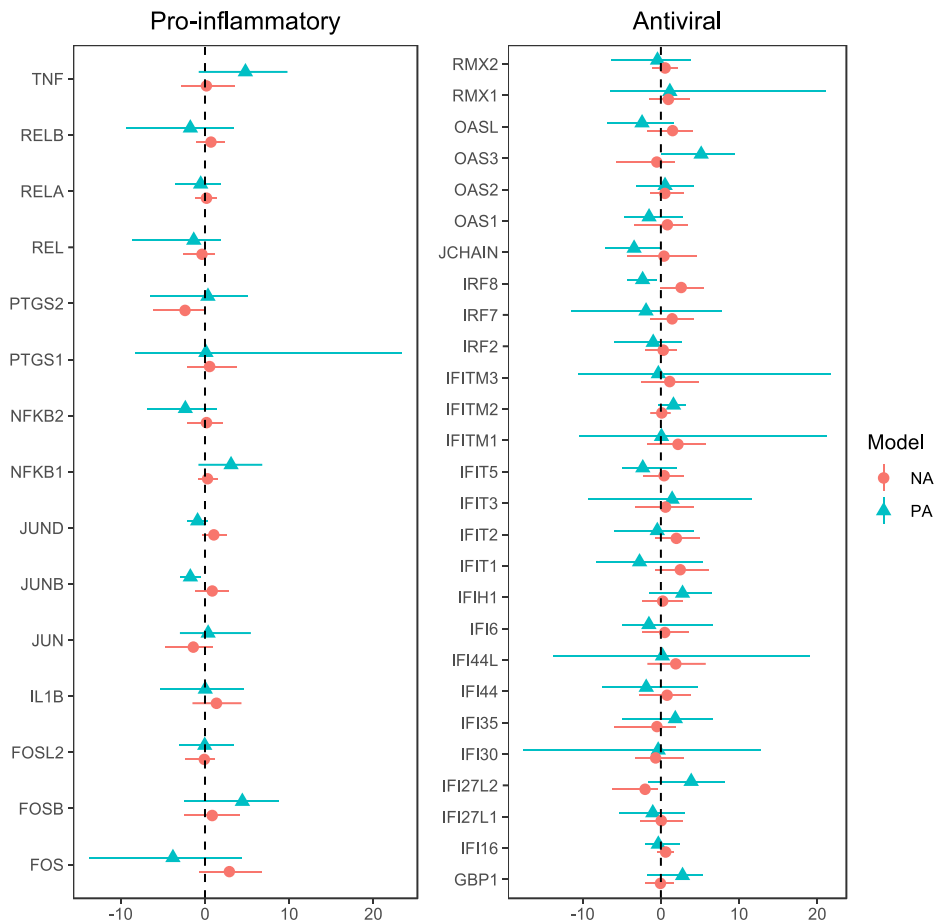

Fig. 2. Individual CTRA Gene Expression Estimates.
Estimates obtained from constructed MSEMs for each individual CTRA gene expression score. Blue triangles indicate gene estimates for positive affective (PA) reactivity models, and red circles indicate gene estimates for negative affective (NA) reactivity models. Whiskers indicate 95% confidence intervals.

This study is novel in that it examined how affective reactivity to daily stressors—which is a relatively more recent method of capturing stress, as compared to chronic or major life stressors (Almeida, 2005; Epel et al., 2018; Minnotte and Yucel, 2018; Pearlin et al., 1981; Wilkinson, 2016)—may contribute to gene regulation. We extended prior work associating affective reactivity to daily stress with elevated pro-inflammatory cytokines among aging adults (Sin et al., 2015b) by linking daily measurements of affect and stress to activation of gene expression. Given that gene expression has been shown to be a mechanism which contributes to such inflammatory responses (Mattos dos Santos, 2020), this study provides insight on pathways by which stress from day-to-day life experiences can 'get under the skin' to affect gene expression. These changes in gene expression, in turn, have implications for physiological responses such as multisystem inflammation. Future work in this area should continue to provide an understanding of how day-to-day stress contributes to health for aging adults, a demographic whose share in the U.S. population and other developed countries continues to increase (Kanasi et al., 2016; Lachman et al., 2015; Vespa et al., 2018). Further understanding of daily stress processes that contribute to changes in gene expression and physiological health are especially important given that aging adults tend to be vulnerable to myriad chronic conditions and infections (Infurna et al., 2020; Mueller et al., 2020; Piazza et al., 2013). This line of research can contribute to interventions that target sources of daily stress for aging adults, address management of responses to stress through mindfulness (Grossman et al., 2004; Gunaydin et al., 2016), and potentially lead to development of technology or therapies that regulate gene expression level responses to stressors to improve wellbeing for midlife and older adults.

Our study is not without limitations. First, daily diary measurements and participant blood samples were taken at different times with varying time intervals for each participant. Although we included this time difference as a covariate in our models, and although it was insignificant in all models, this could have been a source of error. Second, our sample was predominantly White, overweight, and affluent. Future work in this area should be aimed at determining if similar associations between affective reactivity and CTRA gene expression are observed in more diverse and underrepresented populations. Finally, our study was not designed to determine the effects of daily stressors and affective reactivity on gene expression measured the same day. Future studies which use both gene expression and stress/affect measurements obtained on a daily basis will be necessary to determine the temporal biological effects of stress and affective reactivity on a daily basis. Additionally, although previous work on the transcriptional response to stress has been conducted in model organisms (Floriou-Servou et al., 2018; Floriou-Servou et al., 2021; von Ziegler et al., 2022) and in humans in laboratory settings (Dieckmann et al., 2020), novel experimental designs will need to be employed in order to determine if daily gene expression changes are observed in response to daily stressors.

Our work adds evidence to the previous body of research regarding interactions between psychological and physiological states, specifically that immune system regulation is connected to intraindividual affective traits such as affective reactivity (Cole, 2014; Cole et al., 2015, 2007; de Kloet et al., 2005; Powell et al., 2013). This is evidenced by our findings that greater decreases in PA in the presence of daily stressors is associated with increased pro-inflammatory gene expression, specifically for the transcription factor *JUNB*. We hypothesize that overexpression of *JUNB* may be a mechanistic link between the previously detected association of stress regulation and systemic markers of inflammation (Sin et al., 2015b). Future work ought to be directed toward replicating our findings, probing the mediating role of *JUNB* in the association of stress regulation and inflammation, and testing for associations between PA/NA reactivity and stress response-related genes such as *NR3C1*, *FKBP5* and *ADRB2*.

Declaration of Competing Interest

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

Data availability

Data is publicly available through the MIDUS project (https://midus.wisc.edu/)

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2023.09.025.

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