Full Length Article

Subjective arousal and perceived control clarify heterogeneity in inflammatory and affective outcomes

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ABSTRACT

Only a portion of individuals experiencing chronic stress and associated increases in inflammation go on to develop pathological elevations in mood and anxiety symptoms. Some prevailing models suggest that the outcomes of chronic stress may largely depend on individual differences in perceived control. In the current study, we used this theoretical framework to disambiguate the influence of autonomic arousal and perceived control on inflammatory and psychological outcomes in a large sample of adults from the Midlife in the United States dataset (wave 2; MIDUS-2) (Final N = 1030), and further replicated our approach in a second (MIDUS-Refresher) cohort (Final N = 728). Using k-means clustering we created subgroups systematically differing in subjective arousal (high/low) and perceived control (low/high) and compared these subgroups on inflammatory markers and psychological outcomes. Overall results showed that individuals in the high subjective arousal subgroups had higher levels of IL-6, CRP, and FIB, independent of level of CNTL. However, distinctive, and pathological psychological symptom patterns became more apparent when individuals were characterized by both subjective arousal and perceived control. These findings suggest that subtyping individuals based on subjective arousal and perceived control can help us disentangle pathological versus adaptive mental health outcomes in those with co-occurring inflammation and may help identify those vulnerable to psychopathology in the context of physical or psychological stressor exposure.

1. Introduction

It has been appreciated for some time now that physical and psychological stress can trigger innate immune responses leading to systemic inflammation (Glaser and Kiecolt-Glaser, 2005; Simons et al., 2017; Steptoe et al., 2007). Chronic inflammation has been linked to unfavorable medical consequences such as immune suppression, insulin resistance, and poor cardiovascular health (Taylor, 2010; Koolhaas et al., 2011). Growing evidence further suggests that inflammatory markers such as C-reactive protein (CRP) and interleukin (IL)-6 also relate to the pathophysiology of several psychiatric conditions, including mood and anxiety disorders (among others) (Howren et al., 2009; O'Donovan et al., 2010; Felger and Treadway, 2016; Won et al., 2016; Miller and Raison, 2016). While only a subset of those suffering from these psychiatric conditions demonstrate elevations in pro-inflammatory markers, those who do report higher rates of co-occurring chronic inflammation are less

responsive to first-line treatments for mood and anxiety-related symptoms (Michopoulos et al., 2015; Miller et al., 2013; Miller and Raison, 2015). Higher inflammatory marker levels are not uniquely observed in specific diagnostic groupings and can often be associated with different symptom domains, thereby limiting their diagnostic and mechanistic specificity. Furthermore, elevations in inflammatory marker levels are not necessarily indicative of longer-term stress-related pathology. For example, elevations in IL-6 can have both pro- and anti-inflammatory effects depending on its specific mechanism of action (Scheller et al., 2011). Consistent with this, only a subset of rodents and humans who experience chronic stress display unfavorable affective and behavioral outcomes such as social defeat, learned helplessness, and mood/anxiety disorders (Hodes et al., 2014; Ambrée et al., 2018; Kunz-Ebrecht et al., 2003; Pfau and Russo, 2015). It is therefore relevant to understand not only the factors that identify who might develop inflammation-related psychiatric symptoms within diagnostic groupings, but also the

moderators of risk for pathological versus adaptive stress-related psychiatric outcomes across the general population. Accordingly, the purpose of the work outlined here is to systematically evaluate individual difference factors that may relate to inflammatory outcomes as well as theoretically relevant sequelae such as depression and anxiety.

One proposed mechanism by which stress triggers inflammation and associated pathological outcomes is through activation and subsequent dysregulation of the sympathetic nervous system (SNS) (Won and Kim, 2016; Jänig, 2014; Pongratz and Straub, 2014; Chobanyan-Jürgens and Jordan, 2015; Acabchuk et al., 2017; Glaser and Kiecolt-Glaser, 2005). However, like inflammatory markers, measures of SNS activation or autonomic dysregulation (e.g. self-reported autonomic arousal, cortisol, heartrate, skin conductance) lack the specificity necessary to distinguish between noxious and favorable experiences and outcomes. For example, elevations in the physiological measures described above are also observed preceding or during activities that promote healthy/desirable outcomes, such as sex or exercise (Koolhaas et al., 1997; Bronson and Desjardins, 1982; (Bonilla-Jaime et al., 2006); Wirth and Schultheiss, 2006). Increased autonomic arousal also promotes activation of adaptive immune cells (Kenney and Ganta, 2014), which are believed to prepare and protect against stress in the future (Lewitus and Schwartz, 2009) by triggering changes in metabolic, cardiovascular, and neural systems to support adaptive behavioral responses during periods of high stress (McEwen and Wingfield, 2003; De Kloet, Joels and Holsboer, 2005). Thus, neither autonomic arousal nor immune markers serve as reliable or domain specific markers of pathological outcomes of stress, including psychopathology. These ideas also suggest that environmental or internal (cognitive) factors may help to explain the variability in inflammation and affective outcomes observed in relation to high reported autonomic arousal.

Recent theoretical models, primarily developed in rodents, have identified uncontrollability, or the belief that stressors or outcomes cannot be predicted or regulated, as a critical factor leading to maladaptive behavioral outcomes of SNS activation and stress (Koolhaas et al., 2011; Dickerson and Kemeny, 2004; Foa et al., 1992; Elliot et al., 2018). In rodents, stressor controllability reduces the duration, although not the magnitude of SNS response to environmental stressors (Koolhaas et al., 2011), minimizing the chronicity of heightened arousal and associated immune response. Controllable versus uncontrollable shock also leads to greater accumulation of adaptive immune cells during injury or pathogen exposure (Ciavarra et al., 2018). These cells increase the expression of brain-derived neurotrophic factors (BDNF), which may protect against inflammation-related excitotoxicity (Yang et al., 2015; Kerschensteiner et al., 1999), and reduce susceptibility to depressive behaviors (Banasr et al., 2011). However, some studies also report that high relative to low perceived control directly limits the production of inflammatory markers in the presence of an aversive stimulus (Gülpinar et al., 2004; Dang et al., 2019), making it unclear whether perceived control and anxious arousal have shared or unique effects on inflammatory levels.

Perceived control has been linked with increased positive affect (Bogdan et al., 2012; MacAulay et al., 2014), greater motivation (Moller et al., 2006; Patall et al., 2008; Reeve et al., 2003) and improved response to aversive stimuli (Bhanji and Delgado, 2014; Kerr et al., 2012; Legault et al., 2012; Maier et al., 2015). For example, in humans, higher perceived control has been shown to facilitate greater persistence amidst failure during a frustrating behavioral task (Bhanji and Delgado, 2014). In contrast, stress-related autonomic activation is typically associated with increases in negative mood and feelings of anxiety.

These findings suggest that both perceived control and autonomic arousal may influence inflammatory, behavioral, and emotional outcomes, although through potentially distinct mechanisms. In humans, there is little research on the combined and unique effects of autonomic arousal and perceived control on inflammatory and affective outcomes in the general population. Elucidating the specific contribution of these risk and resilience factors can improve our understanding of the effect of

maladaptive stress responses on mental health and inflammatory outcomes. In the long term, this may improve the identification of which individuals are at greatest risk for negative health outcomes linked to stress in ambulatory and clinic settings.

To clarify the distinct and combined contributions of autonomic arousal and perceived control on inflammatory and mental health outcomes, the current study used two large samples of data (N = 1030 and replication sample of N = 728) from the Midlife in the United States (MIDUS) study to create subgroups (*k* means clustering) that differed in subjective measures of 1) autonomic arousal and 2) perceived control. Given the relative novelty of our subgrouping approach and expectations of smaller effect sizes due to larger sample size, we repeated our study in a second, more diverse sample to determine the reliability/replicability of our approach and potential findings. Subgroups created in each dataset were used to systematically probe the unique and combined contributions of arousal and perceived control on proinflammatory marker levels and affective symptoms. In light of evidence suggesting that measures of autonomic arousal, including subjective measures, are associated with greater proinflammatory activity, we hypothesized that individuals in the high (but not low) subjective arousal subgroups would show elevated concentrations of proinflammatory markers (e.g. IL-6, CRP). Given mixed findings on the influence of perceived control on proinflammatory cytokine levels, we also tested whether level of perceived control independently or through interactions with subjective arousal accounted for additional variance in these markers. We also predicted that individuals reporting high arousal would report poorer affective outcomes across multiple domains including depressive distress, anxious distress, loss of interest and positive affect. Further, consistent with prevailing models of pathological stress in rodents (Koolhaas et al., 2011), we predicted that individuals in the high arousal and low perceived control subgroup would have the poorest affective outcomes when compared to all other subgroups. Unique to our study, we also tested whether level of perceived control impacted symptoms at low subjective arousal. Finally, to link findings to diagnostic pathology (above and beyond affective symptoms), we conducted several exploratory analyses to examine whether subgroups differed on risk for psychiatric disorders.

2. Methods

2.1. Data

We used publicly available data from the survey and biomarker sessions of the MIDUS study, a national multi-site longitudinal study of health and well-being (https://midus.wisc.edu/; Radler, 2014). The data reported here were drawn from the first follow-up of the original sample (MIDUS-2), which was collected between 2004 and 2009. To probe the replicability of our method and results, we additionally used data from a second separate cohort of participants (collected between 2011 and 2016) that paralleled the design and protocol of the MIDUS-2 dataset (MIDUS Refresher; MIDUS-R). We included participants who had complete data for all primary self-report measures and inflammatory markers of interest. Participants are described separately for each dataset below. Supplementary Table 1 summarizes which session (survey or biomarker) each variable was collected during.

Of the 1255 individuals who participated in the MIDUS-2 biomarker project, 1054 had data from the survey session as well. Of these 1054 participants, 1030 (Female = 560, Male = 470) had complete data for all measures of interest. Participants in this final subsample were between the ages of 35 and 86 (M_{Age} = 57.96; SEM_{Age} = 0.360). On average, data for the biomarker session was collected 25.85 months after survey session data collection (SEM_{Lag} = 0.460; $Range_{Lag}$ = 0–62 months) (Supplementary Table 2). Of the 863 individuals who participated in the MIDUS-R biomarker project, 746 had data from the survey session as well. Of these 746 participants, 728 (Female = 361, Male = 367) had complete data for all primary measures of interest. Participants in this final subsample were between the ages of 26 and 78 (M_{Age} = 53.53;

SEM_Age = 0.507). On average, data for the biomarker session was collected 21.17 months after survey session data collection (SEM_Lag = 0.327; Range_Lag = 6–52 months) (Supplementary Table 2). See Supplementary Table 2 in results for further sample characteristics and between sample differences on variables of interest.

We initially planned to include age (Z), sex, and lag (Z) in all primary models. Based on findings suggesting a causal relationship between metabolic syndrome and inflammation (Ellulu et al., 2017), we did not plan to include BMI as a covariate in the inflammatory markers model.

Due to observed differences between subgroups in each sample (i.e. collinearity of planned covariates with our subgroups), age, sex, and BMI cannot be reliably included in our primary GLM (see results section for both samples). This choice was due to evidence suggesting that between group differences on within group covariates can substantially reduce power, bias estimates (e.g. exaggerate the effect of sex for one subgroup with higher female to male ratio, while minimizing it in others), and introduce spurious effects (Schneider et al., 2015; see also FDA adopted ICH E9 Statistical Procedures for Clinical Trials). Instead, we include covariates and relevant subgroup * covariate interactions in a second analysis to test the sensitivity of any findings and include these results in the supplemental materials (Miller and Chapman, 2001).

2.2. Measures

2.2.1. Primary self-report measures

Mood and Anxiety Symptom Questionnaire (MASQ). Participants completed a 62-item version of the MASQ, a dimensional measure of affective symptoms based on a tripartite model of anxiety and depression (Clark and Watson, 1991). This measure includes five subscales that did not include any overlapping items: depressive distress (DD), anxious distress (AD), loss of interest (LI), high positive affect (PA), and anxious arousal (AA). Participants rated how much they experienced each item during the past week on a Likert scale ranging from 1 (not at all) to 5 (extremely). The AA subscale measures intensity of self-reported physiological symptoms associated with autonomic arousal (e.g. "was trembling or shaking", "felt dizzy or lightheaded" (Clark and Watson, 1991). We used the sum of items on this scale as our index of subjective autonomic arousal (Larson et al., 2007). Symptoms from the AA scale index physiological burden more generally, and do not refer to the valence (positive/negative), or effect (adaptive/maladaptive) of these symptoms (Larson et al., 2007). Cronbach's alpha for this scale was acceptable in both samples (MIDUS-2 α = 0.777; MIDUS-R α = 0.761).

Items from the DD subscale assesses symptoms linked to depression and low mood (e.g. "felt sad", "felt like a failure") (MIDUS-2 Chronbach's α = 0.903; MIDUS-R Cronbach's α = 0.873). The AD subscale measures discomfort typically associated with anxiety (e.g. "felt nervous", "felt uneasy") (MIDUS-2 Chronbach's α = 0.790; MIDUS-R Cronbach's α = 0.799). LI measures non-specific lack of motivation typical in patients with depression (e.g. "felt really slowed down", "felt nothing fun/interesting to do") (MIDUS-2 Chronbach's α = 0.813; MIDUS-R Cronbach's α = 0.797). Finally, the PA subscale includes items associated with the experience of positive emotions and optimism (e.g. "Felt really happy", "Looked forward with enjoyment") (MIDUS-2 Chronbach's α = 0.93; MIDUS-R Cronbach's α = 0.93). We used the standardized sum of items on the DD, AD, LI, and PA subscales as our measure of affective outcomes for various subdomains of positive and negative affect. Higher scores in DD, AD, and LI and lower scores in PA correspond with greater symptom severity. As the MASQ AA subscale served as an independent variable and other MASQ subscales served as dependent variables, it is important to note that none of these subscales contain overlapping items.

Sense of Control Scale (SCS). The SCS (hereafter CNTL) is a 12-item measure with two subscales (personal mastery and perceived constraints), developed by Lachman and Weaver (1998). Personal mastery refers to self-efficacy/effectiveness in reaching goals (e.g. "I can do just about anything I really set my mind to"). The perceived constraints subscale measures the extent to which factors beyond one's control contribute to experienced outcomes (e.g. "What happens in my life is often beyond my control"). Participants rated items on a Likert scale ranging from 1 (Strongly Agree) to 7 (Strongly disagree). Personal Mastery items were reverse scored so that higher total scores reflected greater perceptions of control. Composite scores were created by calculating the mean of all 12 items and then mean standardizing them separately within each dataset. Cronbach's alpha for this composite was good (MIDUS-2 α = 0.79 and MIDUS-R α = 0.81).

2.2.2. Inflammatory markers

Our analyses focused on IL-6, CRP, and Fibrinogen (FIB) as indicators of pro-inflammatory activity. These markers are linked to higher levels of inflammation and were selected based on their consistent association with symptoms of psychopathology in the literature (See Supplementary Materials for additional descriptions and for other available markers used in exploratory analyses). Both Kolmogorov-Smirnov and Shapiro-Wilk tests of normality suggested significant deviations from the normal distribution for all markers (all positively skewed; all ps < .001). Qualitative inspection of normal and detrended Q-Q plots, and stem-and-leaf plots provided evidence for considerable positive skew for IL-6 and CRP, which were thus natural log transformed, consistent with common practice. Post-transformation, plots were visually inspected to ensure normal distribution. All measures were standardized separately to each dataset mean for ease of visualization and due to differing units of measurement.

2.3. Data analysis

2.3.1. Subgrouping using K-Means clustering

To systematically probe how inflammatory and affective outcomes varied as a function of individual differences in either or both AA and CNTL domains, our goal was to create four subgroups based on a 2 × 2 design of high/low AA and concurrent high/low CNTL. Due to the skewed distribution of data for both AA (positive skew) and CNTL scales (negative skew), and no formally defined clinically relevant cutoffs for these measures, we used k-means clustering rather than splitting data by a measure of central tendency or setting an arbitrary cut-off. Due to skews in data, treating these variables as continuous rather than categorical would bias results towards the most populous end of the distribution while clinically relevant information is often found in the smaller percentage of the population that falls in the tail-end (e.g. statistical rarity). This partially data-driven method also ensured that results were agnostic with respect to diagnostic categorization, focusing instead on naturally occurring variability in the dimensions of interest. K-means clustering is an unsupervised machine learning algorithm for separating data (in this case individual participants) into *k* number of clusters (or groups) given a set of data points (e.g. behavioral, self-report, physiological measures). The number of groups that are specified *a priori* may be for a combination of both theoretical and data-driven reasons (Kaufman and Rousseeuw, 1990). Well-defined clusters are those that generally have high intra-cluster similarity (low within cluster variance) and low inter-cluster similarity (high between-cluster variance). All clustering and statistical tests were conducted in SPSS (IBM SPSS Statistics Subscription, Build 1.0.0.1118, 64-bit edition, IBM Corp, 2018). We evaluated clustering solutions using the silhouette function in MATLAB (Mathworks, R2016b; Supplemental Fig. 1). Due to differences in measurement scales, we mean standardized AA and CNTL scores (Z) prior to clustering. There was a moderate but significant negative correlation between AA and CNTL in the MIDUS-2 (rho = −0.277, p < .001) and MIDUS-R samples (rho = −0.294, p < .001).

To create subgroups based on AA, we used k-means clustering with squared Euclidean distance as our distance metric, setting the number of

iterations to ≤100 (or until change in centroids converged to zero). To maximize the between group differences on this variable and create high and low AA subgroups, we opted to define k = 2 in our final model (See supplementary methods (1.2) for further detail on quality control and rationale for this and other related decisions). We repeated the same procedure using CNTL scores to create k = 2 groups that differed maximally on perceived control (high and low). The overlap of AA and CNTL clusters (their interaction) defined the four final subgroups (high AA/low CNTL, high AA/high CNTL, low AA/low CTNL, and low AA/high CNTL). We denote these subgroups as AA + or AA- (for high and low AA) and CNTL + or CNTL- (for high and low perceived CNTL) (See Supplementary Fig. 2). For methods and results testing for differences between subgroups on participant characteristics (age, BMI, income, race, lag between sessions, and sex) see Supplementary materials.

2.3.2. Statistical analysis

To test hypotheses related to associations between perceived control and self-reported arousal with individual differences in pro-inflammatory activity and affective outcomes, separate univariate GLMs (Type III Sums of Squares) probed main effects and interactions of AA and CNTL factors on inflammatory marker levels and affective domains. For significant univariate effects, if assumptions were met for parametric statistical tests, we used post-hoc pairwise mean difference tests to probe these effects (Bonferroni corrected). To reduce Type 1 error in GLM models, we took a conservative approach and used a Bonferroni corrected threshold of alpha = .0167 for inflammatory markers (IL-6, CRP, and FIB), alpha = .025 for negative affect variables (AD and DD), and 0.025 for variables related to anhedonia (LI and PA). When assumptions were not met, we used non-parametric tests (Kruskal-Wallis and Dunn's Bonferroni correction for post-hoc pairwise tests). To determine how each subgroup compared to the entire sample, we compared estimated marginal means for each subgroup against the grand mean of the sample. This comparison was important in determining the clinical relevance of observed effects.

2.3.3. Exploratory analyses

To explore the association between the characteristics of identified subgroups and mental health risk, we followed up our main analyses with several exploratory analyses using data available on the prevalence of these outcomes in each sample. We used data on whether participants met clinical criteria for depression, panic disorder, and generalized anxiety (yes/no) based on responses to DSM-IV symptom cluster questions gathered via phone interview. We also examined self-reported responses (yes/no) to the question "Have you had depression, anxiety, or any other emotional disorder over the past 12 months?" (survey session; 0% missing in MIDUS-2, 1.5% missing in MIDUS-R), and "Have you ever had depression?" (biomarkers session; 0.002% missing in MIDUS-2, 0% missing in MIDUS-R). For the latter question, if a participant responded "Borderline" or "Unsure", we took a conservative approach and re-coded these responses as "No". Chi-squared tests were used to determine whether there was a significant effect of subgroup on these dependent variables. We computed a prevalence ratio (PR) by dividing the point prevalence (of "yes" responses; (Y)) for each subgroup (G) and each item, by the point prevalence across the entire dataset (D) for that item. This value allows us to quantify the degree to which each subgroup disease burden differs from what is expected from the total sample, and the direction of this difference. Given that the prevalence of several psychiatric disorders (e.g. Depression) may differ across sexes, we computed PRs separately for males and females. Values less than one suggest a reduced prevalence, those equal to one suggest prevalence is similar to sample prevalence, and values greater than one suggest a greater prevalence relative to the total sample [Eq. (1)].

$$PR = \frac{P(Y|G)}{P(Y|D)}$$ [Eq. 1]

3. Results

3.1. Dataset and subgroup characteristics

A more detailed summary of differences between the MIDUS-2 and MIDUS-R datasets (Supplemental Table 2) and between subgroups within each dataset is presented in the supplementary materials (Supplemental Fig. 2, Supplemental Tables 3 and 4). Despite clustering each dataset separately, there were no significant differences between MIDUS-2 and MIDUS-R in the proportion of individuals who fell into each respective subgroup (χ^2 = 0.354, p = .950). Most participants in each dataset fell into the AA-/CNTL + subgroup (MIDUS-2 = 58.83%; MIDUS-R = 59.34%), followed by the AA-/CNTL-subgroup (MIDUS-2 = 24.7%; MIDUS-R = 24.14%), AA+/CNTL-subgroup (MIDUS-2 = 9.32%; MIDUS-R = 8.52%), and the AA+/CNTL + subgroup (MIDUS-2 = 7.08%; MIDUS-R = 7.01%).

Overall, results indicated that in both MIDUS-2 and MIDUS-R samples, subgroups differed on sex, age, BMI, and income, while differences in race were only observed in the MIDUS-R sample (See Supplementary Tables 3 and 4). This sample included a larger percentage of participants oversampled from urban populations, which is reflected in the differences between samples on race.

3.2. Individual differences in inflammation by subgroup

Zero order correlations between IL-6, CRP, and FIB can be found in the supplementary results section (Supplementary Materials).

Above and beyond effects associated with all other predictors and lag, there was a small but significant main effect of AA level on Log IL-6 (Z) (F(1,1025) = 13.07, p < .001, η_p^2 = .013) and Log CRP (Z) (F(1,1025) = 10.97, p = .001, η_p^2 = .011) in the MIDUS-2 sample (Fig. 1). These effects were replicated in the MIDUS-R sample (Fig. 1; IL-6 F(1,723) = 10.17, p = .001, η_p^2 = .014; CRP F(1,723) = 11.77, p = .001, η_p^2 = .016). There was an additional significant main effect of AA subgroups on FIB (Z) in the MIDUS-R sample (F(1,723) = 13.92, p < .001, η_p^2 = .019. There was no significant main effect of CNTL or AA*CNTL interaction on any of the markers. Consistent with our hypothesis, individuals in the AA + subgroup had significantly higher inflammatory marker levels than those in the AA-subgroup (Fig. 1). Findings suggest a reliable (replicated in both samples) unique effect of subjective arousal on inflammatory markers IL-6 and CRP that does not depend on level of perceived control.

3.3. Differences among subgroups in affective domains

3.3.1. Subgroup differences in negative affective domains

MASQ Depressive distress and MASQ anxious distress scores were moderately and significantly correlated in each sample (MIDUS-2 Spearman's rho = 0.619, p < .001; MIDUS-R Spearman's rho = 0.630, p < .001). Assumptions of equality of variance (Levene's test) and covariance (Box's Test and visual inspection of variance spread plots) were not met (all ps < .001). Given that these tests are highly sensitive to unequal sample sizes between factor levels, we ran both parametric (separate univariate GLMs) and non-parametric (Kruskal-Wallis) tests. There were no qualitative differences in the tested effects and as such we report the results of the parametric tests to simplify interpretation of the findings. Violin plots summarizing observed measures of central tendency and distributions (optimally smoothed rotated kernal density plots) of DD and AD scores in each subgroup are depicted in Fig. 2 for both samples (See Table 1 for parameter estimates and associated effect sizes for all predictors in each model).

In the MIDUS-2 sample, there was a significant AA*CNTL interaction on standardized (Z) depressive distress scores (F(1,1025 = 20.163, p < .001, η_p^2 = .019; Full model: adj. R^2_{DD} = 0.203) and anxious
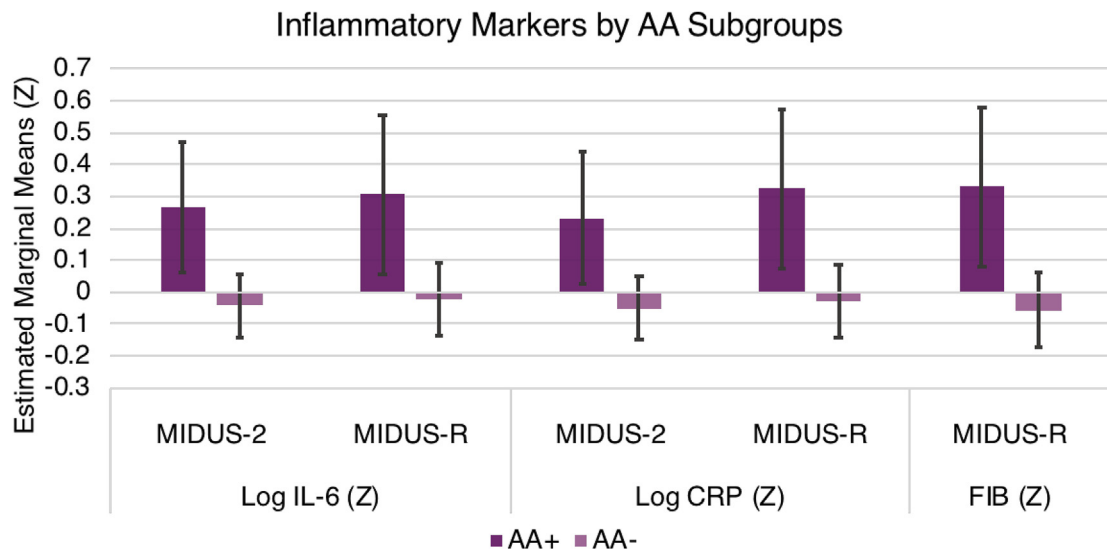
Fig. 1. Error bars denote 99.2% CI (alpha = .008). Estimated marginal means for the high arousal group were also significantly greater than the grand mean. All p's </ = .001, MIDUS-2 IL-6 Effect Size (η_p^2) = 0.013; MIDUS-R Effect Size (η_p^2) = 0.014. MIDUS-2 CRP Effect Size (η_p^2) = 0.011; MIDUS-R Effect Size (η_p^2) = 0.016. MIDUS-R FIB Effect Size (η_p^2) = 0.019.
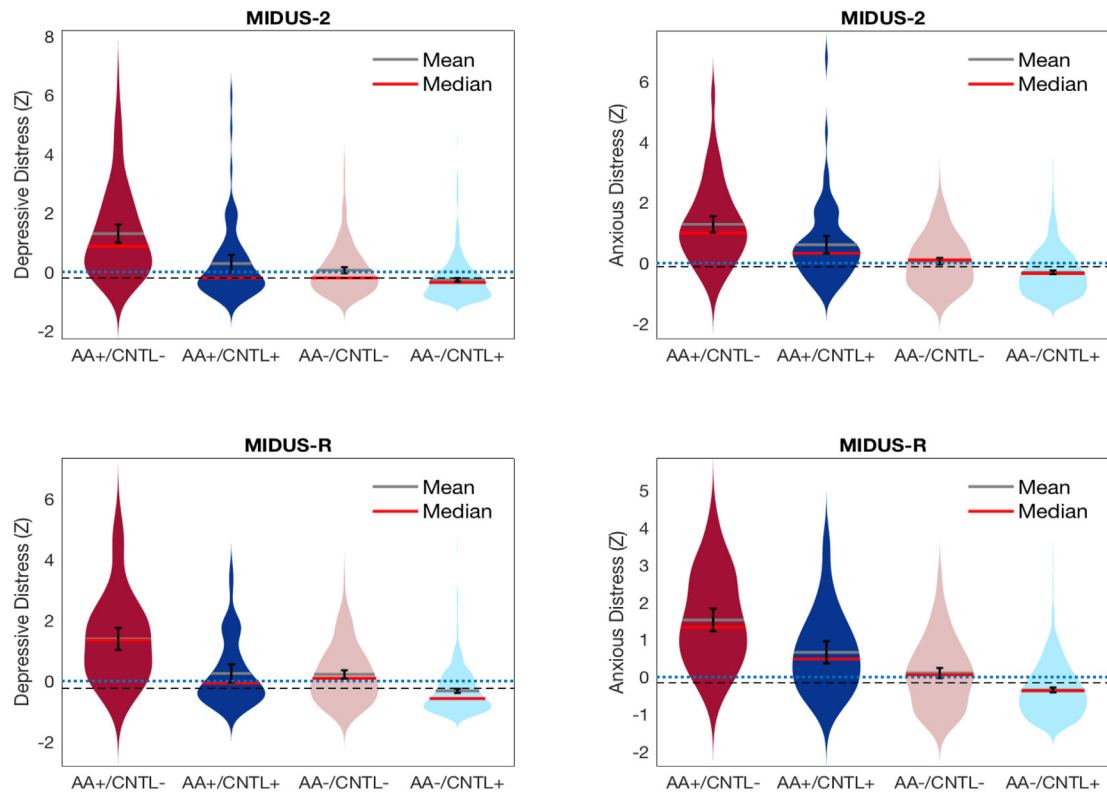

Fig. 2. Violin plots above show rotated kernel density plots (smoothing kernel optimized for each subgroup). These plots show the distribution of standardized raw depressive distress and anxious distress scores for each subgroup, the mean of each subgroup in red, the median of each subgroup in gray, the 95% CI of the mean (error bars), and a blue dotted line depicting the total sample mean, and a black dashed line representing the median of the sample. Top Left: MIDUS-2 subgroup distributions for depressive distress scores (Z). Top Right: MIDUS-2 subgroup distributions for anxious distress scores (Z). Bottom Left: MIDUS-R subgroup distributions for depressive distress scores (Z). Bottom Right: MIDUS-R subgroup distributions for anxious distress scores (Z). In both samples, a larger proportion of the distribution for the AA+/CNTL-subgroup falls above the mean and median compared to all other subgroups for depressive distress and anxious distress. Non-overlapping error bars depict significant differences in means (p < .05). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

distress (Z) scores (F(1,1025 = 4.110, p = .043, η_p^2 = .004); Full model: adj. R^2_{AD} = 0.232). The AA* CNTL interaction on AD did not survive our corrected alpha threshold of 0.025. These results were largely replicated

in the MIDUS-R sample (DD F(1,723) = 10.68, p = .001, η_p^2 = .015, Full Model adj. R^2_{DD} = 0.243; Full Model: AD F(1,723) = 5.58, p = .018, η_p^2 = .008, Full Model adj. R^2_{AD} = 0.302). The AA*CNTL interaction

Table 1
Parameter estimates for negative affect symptom domains.

Dependent Variable	Sample	Predictor	β	Std. Error	t	p	97.5% Confidence Interval		Effect Size (η_p^2)
							Lower Bound	Upper Bound	
Depressive Distress (Z)	MIDUS-2	Intercept	−0.265	0.036	−7.301	***	−0.346	−0.183	0.049
		Lag(Z)	4.224×10^{-5}	0.028	0.002	0.999	−0.062	0.063	0.000
		AA+ = 1	0.551	0.111	4.976	***	0.302	0.799	0.024
		CNTL- = 1	0.323	0.067	4.847	***	0.173	0.473	0.022
		AA+/CNTL- = 1	0.691	0.154	4.490	***	0.346	1.037	0.019
	MIDUS-R	Intercept	−0.325	0.042	−7.755	***	−0.419	−0.231	0.077
		Lag(Z)	0.069	0.032	2.152	0.032	−0.003	0.142	0.006
		AA+ = 1	0.576	0.129	4.472	***	0.287	0.865	0.027
		CNTL- = 1	0.549	0.077	7.151	***	0.377	0.721	0.066
		AA+/CNTL- = 1	0.593	0.181	3.267	0.001	0.185	1.000	0.015
Anxious Distress (Z)	MIDUS-2	Intercept	−0.304	0.036	−8.541	***	−0.384	−0.224	0.066
		Lag(Z)	0.003	0.027	0.100	0.920	−0.059	0.064	0.000
		AA+ = 1	0.912	0.109	8.400	***	0.668	1.156	0.064
		CNTL- = 1	0.369	0.065	5.646	***	0.222	0.516	0.030
		AA+/CNTL- = 1	0.306	0.151	2.027	0.043	−0.033	0.645	0.004
	MIDUS-R	Intercept	−0.346	0.040	−8.604	***	−0.436	−0.256	0.093
		Lag(Z)	0.032	0.031	1.034	0.302	−0.038	0.102	0.001
		AA+ = 1	1.010	0.124	8.165	***	0.732	1.288	0.084
		CNTL- = 1	0.458	0.074	6.210	***	0.292	0.624	0.051
		AA+/CNTL- = 1	0.412	0.174	2.362	0.018	0.020	0.803	0.008

***p < .001.
1 = yes.
Intercept represents the marginal mean of the AA-/CNTL- (reference) subgroup.

survived our corrected alpha threshold for both DD and AD in the MIDUS-R sample. Each reported effect is unique above and beyond the variance accounted for by main effects and lag in the model.

Results show that CNTL level moderates (Baron and Kenny, 1986) DD (Z) at high and low arousal, with a substantially greater effect at high arousal. Those in the AA+/CNTL-subgroup (M = 1.30, SEM = 0.091, 97.5% CI = 1.095–1.505) have significantly higher estimated marginal mean DD (Z) relative to the grand mean and all other subgroups. DD marginal means for the AA+/CNTL+ (M = 0.286, SEM = 0.105, 97.5% CI = 0.051-0.520) and AA-/CNTL-subgroups (M = 0.058, SEM = 0.056, 97.5% CI = −0.067-0.184) were not statistically different from each other. Mean DD (Z) for the AA-/CNTL + subgroup was significantly lower than the sample mean and mean of both AA + subgroups (M = −.265, SEM = 0.036, 97.5% CI = −0.346 - - 0.183) These results were consistent across both MIDUS-2 and MIDUS-R samples and suggest that while high arousal and low control each independently contribute to higher symptoms of depressive distress, their combined effect leads to a much greater severity compared to the overall sample and all other subgroups (See Supplemental Fig. 4 for graph of estimated marginal means for DD (Z) and AD (Z) for each sample).

While low CNTL seemed to affect AD and DD similarly, high CNTL had a weaker moderating effect on AD (Z) when AA was high, than it did on DD (Z) at high AA, suggesting that increased CNTL may have a specific beneficial effect on depressive symptoms when AA is high. All subgroups differed significantly from each other on estimated marginal means for Anxious Distress (Z). The AA+/CNTL-subgroup had the highest estimated means for AD (Z) (M = 1.283, SEM = 0.089, 97.5% CI = 1.083–1.505), followed by the AA+/CNTL+ (M = 0.608, SEM = 0.103, 97.5% CI = 0.378-0.838), AA-/CNTL- (M = 1.283, SEM = 0.089, 97.5% CI = −0.058 - 0.188), and AA-/CNTL + subgroups (M = −0.304, SEM = 0.036, 97.5% CI = −0.384 - -.224). Both AA + subgroup means (Z) were significantly greater than the grand mean, and only the AA-/CNTL + subgroup had estimated means significantly below the grand mean in both samples.

3.3.2. Subgroup differences in domains of anhedonia

Standardized MASQ Loss of Interest and MASQ Positive Affect scores were moderately and significantly correlated in each sample (MIDUS-2 Spearman's rho = −0.479, p < .001; MIDUS-R Spearman's rho = −0.440, p < .001). Violin plots summarizing the distribution (optimally smoothed

rotated kernel density plots) with measures of central tendency for observed standardized scores in each subgroup for LI (Z) and PA (Z) are depicted in Fig. 3 for both samples (See Table 2 for parameter estimates for all predictors in each model).

In the MIDUS-2 sample, there was a significant AA*CNTL interaction on standardized (Z) Loss of Interest (LI) scores (F(1,1025 = 26.70, p < .001, η_p^2 = .025; Full model: adj. R^2_{LI} = 0.261). These results were replicated in the MIDUS-R sample (F(1723 = 5.64, p = .008, η_p^2 = .008; Full model: adj. R^2_{LI} = 0.265). Like findings reported for DD (Z), the level of CNTL moderates LI differently across high and low arousal, with a substantially greater effect at high arousal. In the MIDUS-2 sample, the AA+/CNTL-subgroup had significantly higher estimated marginal means compared to the sample grand mean and all other subgroups (M = 1.468, SEM = 0.088, 97.5% CI = 1.271–1.665). Marginal means for the AA+/CNTL+ (M = 0.325, SEM = 0.101, 97.5% CI = 0.099-0.551) and AA-/CNTL-subgroups (M = 0.074, SEM = 0.054, 97.5% CI = −0.047-0.195) were not statistically different from each other. Mean LI (Z) for the AA-/CNTL + subgroup was significantly lower than the sample mean and mean of both AA + subgroups (M = −0.303, SEM = 0.035, 97.5% CI = −0.381 - - 0.225). These results were replicated in the MIDUS-R sample (See Supplementary Fig. 5 for graph of marginal means for both samples).

For Positive Affect (Z), there were significant unique main effects of AA (F(1,1025 = 23.237, p < .001, η_p^2 = .0211) and CNTL (F(1,1025 = 46.074, p < .001, η_p^2 = .043) in the MIDUS-2 sample (Full model: adj. R^2_{PA} = .094). These results were replicated in the MIDUS-R sample (AA F(1723 = 7.66, p = .006, Partial η_p^2 = .010; CNTL F(1,723) = 60.975, p < .001, Partial η_p^2 = .078 Full model: adj. R^2_{LI} = 0.124. The interaction was not significant in either sample (MIDUS-2 p = .443; MIDUS-R p = .216). Overall, both AA + subgroups had lower PA (Z) irrespective of level of CNTL and both CNTL-subgroups had lower PA (Z) irrespective of level of AA. In the MIDUS-2 sample, the AA+/CNTL- and the AA-/CNTL-subgroups had significantly lower estimated marginal mean PA (Z) scores compared to the sample grand mean. The AA+/CNTL-subgroup also had lower mean PA (Z) compared to all other subgroups. Marginal mean PA (Z) scores for each subgroup is as follows: AA+/CNTL- (M = −.718, SEM = 0.097, 97.5% CI = −0.936- -.499), AA+/CNTL+ (M = −0.098, SEM = 0.111, 97.5% CI = −0.348- 0.152), AA-/CNTL- (M = −0.259, SEM = 0.060, 97.5% CI = −0.393- -
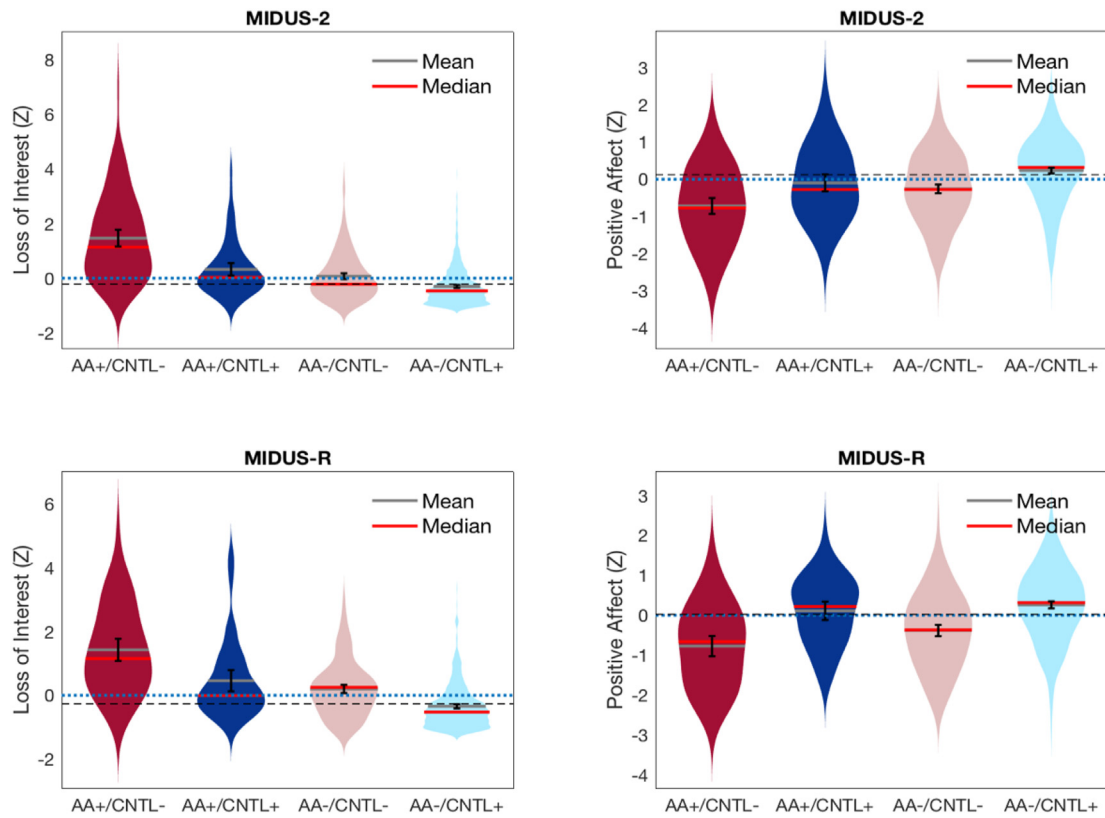
Fig. 3. Violin plots depicted above show rotated kernel density plots (smoothing kernel optimized for each subgroup). These plots show the distribution of standardized raw scores for each subgroup, the mean of each subgroup in red, the median of each subgroup in gray, the 95% CI of the mean (error bars), a blue dotted line depicting the total sample mean, and a black dashed line representing the median of the sample. Top Left: MIDUS-2 subgroup distributions for loss of interest (Z). Top Right: MIDUS-2 subgroup distributions for positive affect (Z). Bottom Left: MIDUS-R subgroup distributions for loss of interest (Z). Bottom Right: MIDUS-R subgroup distributions for positive affect (Z). In both samples, a larger proportion of the distribution for the AA+/CNTL-subgroup falls above the mean and median compared to all other subgroups for loss of interest. In positive affect, a larger proportion of the AA+/CNTL- and AA-/CNTL-subgroups (respectively), fall below the sample mean. Non-overlapping error bars depict significant differences in means (p < .05). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Parameter estimates for anhedonia symptom domains.

Dependent Variable	Sample	Predictor	β	Std. Error	t	p	97.5% Confidence Interval		Effect Size (η_p^2)
							Lower Bound	Upper Bound	
Loss of Interest (Z)	MIDUS-2	Intercept	−0.303	0.035	−8.675	***	−0.381	−0.225	0.068
		Lag(Z)	−0.007	0.027	−0.274	0.784	−0.068	0.053	0.000
		AA+ = 1	0.628	0.106	5.898	***	0.389	0.867	0.033
		CNTL- = 1	0.377	0.064	5.877	***	0.233	0.521	0.033
		AA+/CNTL- = 1	0.765	0.148	5.167	***	0.433	1.098	0.025
	MIDUS-R	Intercept	−0.344	0.041	−8.336	***	−0.437	−0.251	0.088
		Lag(Z)	0.006	0.032	0.191	0.848	−0.065	0.078	0.000
		AA+ = 1	0.802	0.127	6.320	***	0.517	1.088	0.052
		CNTL- = 1	0.545	0.076	7.196	***	0.375	0.715	0.067
		AA+/CNTL- = 1	0.425	0.179	2.375	0.018	0.023	0.827	0.008
Positive Affect (Z)	MIDUS-2	Intercept	0.235	0.039	6.066	***	0.148	0.321	0.035
		Lag(Z)	0.001	0.030	0.027	0.979	−0.066	0.067	0.000
		AA+ = 1	−0.332	0.118	−2.818	0.005	−0.597	−0.068	0.008
		CNTL- = 1	−0.494	0.071	−6.951	***	−0.653	−0.334	0.045
		AA+/CNTL- = 1	−0.126	0.164	−0.768	0.443	−0.494	0.242	0.001
	MIDUS-R	Intercept	0.260	0.045	5.766	***	0.159	0.361	0.044
		Lag(Z)	0.006	0.035	0.182	0.855	−0.072	0.084	0.000
		AA+ = 1	−0.149	0.139	−1.078	0.281	−0.461	0.162	0.002
		CNTL- = 1	−0.642	0.083	−7.768	***	−0.827	−0.456	0.077
		AA+/CNTL- = 1	−0.242	0.195	−1.238	0.216	−0.680	0.197	0.002

***p < .001.

1 = yes; Intercept represents the marginal mean of the AA-/CNTL- (reference) subgroup and coefficients.

0.126), AA-/CNTL+ (M = 0.235, SEM = 0.039, 97.5% CI = 0.148-0.231). The AA+/CNTL+ and AA-/CNTL-subgroups were not statistically different from each other in the MIDUS-2 sample, however in the MIDUS-R sample, those in the AA-/CNTL-subgroup had significantly

lower PA than those in the AA+/CNTL + subgroup. Mean PA (Z) for the AA-/CNTL + subgroup was significantly higher than the sample mean in both samples (See Supplemental Fig. 5 for graph of marginal means for both samples).

3.4. Exploratory analyses: prevalence of chronic pathology

We conducted exploratory chi-squared tests to determine whether the elevations in symptoms reported above translated into subgroup differences in prevalence for diagnosable psychopathology. The 12-month prevalence of anhedonia, anxiety disorder, panic attack, and depressed affect refers to whether participants met DSM-IV clinical criteria for symptoms in that domain at any point during the past year based on questions asked by researchers in the study. The other two variables refer to self-reported diagnoses of depression/anxiety/emotional disorder during the past 12 months, and self-reported diagnoses of depression ever (lifetime). There was a significant effect of subgroup for all variables tested in both MIDUS-2 and MIDUS-R samples (Table 3).

We calculated prevalence ratios for all subgroups against the total sample prevalence and found that in all cases, individuals in the AA+/CNTL-subgroup showed the highest overall prevalence ratios. We depict these prevalence ratios for each sample in Fig. 4 and have included them further separated by sex in the supplementary materials (Supplementary Figs. 6 and 7).

4. Discussion

The principal aim of this study was to test the unique and combined contributions of subjective arousal and perceived control on inflammatory and affective outcomes in a large sample of adults from the general population. Our subgrouping method allowed us to study these effects systematically by creating pairs of subgroups that were homogeneous in one dimension (e.g. subjective arousal) but varied on the other dimension (e.g. perceived control; and vice versa). The subgroupings created in the MIDUS-2 sample were replicated in the separate and more demographically diverse sample from the MIDUS-R, suggesting subgroupings based on high and low levels of subjective arousal and perceived control may reliably represent patterns found in the general population of U.S. adults. Further, the current findings show dissociable effects of subjective arousal and perceived control on inflammatory and affective outcomes. Individual differences in these two domains may help us better understand the risk and resilience factors that contribute to heterogeneity across specific outcome domains. Across both samples and in line with hypotheses, we found evidence that individuals in the high subjective arousal subgroups showed higher proinflammatory marker levels

Table 3
Effect of subgroup on psychopathology.

Psychopathological Domain	Sample	χ^2	Sig. (p)
Anhedonia (12 Months)	MIDUS-2	22.51	p < .001
	MIDUS-R	10.07	p = .018
Anxiety Disorder (12 Months)	MIDUS-2	34.99	p < .001
	MIDUS-R	32.56	p < .001
Panic Attack (12 Months)	MIDUS-2	34.43	p < .001
	MIDUS-R	36.51	p < .001
Depressed Affect (12 Months)	MIDUS-2	99.80	p < .001
	MIDUS-R	36.26	p < .001
Anxiety/Depression/Emotional Disorder (12 Months)	MIDUS-2	73.62	p < .001
	MIDUS-R	72.07	p < .001
Depression Ever (Lifetime)	MIDUS-2	49.07	p < .001
	MIDUS-R	69.71	p < .001

relative to those in the low subjective arousal subgroups and relative to grand means. We tested whether perceived control had a unique main effect or interaction with AA on pro-inflammatory marker levels and found that it did not. However, consistent with evidence from rodent models of pathological stress (Koolhaas et al., 2011), the subgroup expressing high arousal paired with low perceived control showed greater severity in symptoms of mood and anxiety compared to every other subgroup and the sample means. We also found that individuals in either of the low control subgroups showed attenuated positive affect with respect to the overall sample mean (while the high control subgroups did not), suggesting a unique effect of perceived control on reduced hedonic capacity (Bogdan et al., 2012; MacAulay et al., 2014). We demonstrated replicable evidence that individual differences in *both* subjective arousal and perceived control and combinations thereof, revealed distinct patterns of psychopathology-relevant heterogeneity that co-occurred with high and low inflammation. This heterogeneity would have otherwise been masked had either dimension been considered independently.

4.1. Effect of subjective arousal on IL-6, CRP, and FIB

In both samples, we found that those in the high arousal, relative to low arousal subgroups, had higher levels of IL-6 and CRP. These effects largely remained, even after accounting for additional unique variance attributed to age, lag, sex and their subgroup interactions (See Supplementary Results). Of note, from these supplemental analyses, we found an arousal by sex interaction on CRP levels in the MIDUS-2 sample. At low arousal, females showed higher levels of CRP compared to males and no change from low to high arousal while males showed a significant arousal-related increase in CRP levels. CRP levels have been associated with increased risk for cardiovascular pathology among other chronic inflammatory conditions such as arthritis, and there is evidence to support that overall inflammatory pathology in women is more common than in men (Appelman et al., 2014). This effect may be due to dissociable influences of sex hormones, on inflammation (Schmidt et al., 2006) and may suggest one possible reason why females show CRP levels at low arousal, that are comparable to males at high arousal. Duivis and colleagues found that somatic symptoms of patients with depression and anxiety were associated with CRP and IL-6 (Duivis et al., 2013). Additionally, they reported a sex-related interaction with CRP, such that, in males, higher cognitive symptoms of anxiety were associated with CRP levels (but not females). While our high arousal sample (MIDUS-2 = 169 and MIDUS-R = 113) was much smaller than the patient sample in their study (N = 2231), our findings are comparable, confirming the sensitivity of subjective arousal as a predictor of inflammation and of associated sex-related variability.

In the MIDUS-R sample, we additionally found elevated FIB levels in the high, relative to low arousal subgroup. After including covariates in the secondary model (Supplementary Results) the interaction of arousal and sex was significant for FIB in the MIDUS-2 sample. Males showed an arousal-related increase in FIB, while females showed no difference by arousal level and had comparable elevations to males at high and low arousal. In the MIDUS-R sample, this effect was consistent in direction, although not statistically significant. One reason for sex-related discrepancies between samples, may be that the high arousal group had a smaller sample size in MIDUS-R which may have reduced power to reliably detect small multiplicative effects. Fibrinogen is becoming increasingly relevant in the context of psychiatric disorders. For example, in a large sample of 73,367 patients, Wium-Anderson and colleagues found that individuals with higher plasma fibrinogen levels reported that they were more likely to give up, not accomplish tasks, use antidepressants, and were more likely to have a history of hospitalization for depression (Wium-Andersen et al., 2013). Further, Martins-de-Souza and colleagues, found that antidepressant responders versus non-responders had lower levels of fibrinogen alpha protein (Martins-De-Souza et al., 2014).

Prevalence Ratios for Psychopathology by Subgroup

Fig. 4. In both samples, individuals in the AA+/CNTL-subgroup consistently had the highest prevalence ratios. The prevalence of psychopathology in this subsample ranged between 2.2 and 4.9 in the MIDUS-2 and 1.9–4.3 in the MIDUS-R samples. Prevalence ratios for the AA+/CNTL + subgroup ranged between .96 and 1.85 in the MIDUS-2 and 0.67–2.07 in the MIDUS-R sample. For the AA-/CNT-subgroup, prevalence ratios ranged between 0.71 and 2.5 in the MIDUS-2 and 1.01–1.83 in the MIDUS-R samples. The AA-/CNTL + subgroup had prevalence ratios that were all below the sample mean.

Causes of increased autonomic arousal and inflammation outside of aging and explicit disease/illness, include a wide range of psychosocial sources of stress. For example, low socioeconomic status, childhood adversity, loneliness, job loss, and caregiving responsibilities have all been linked to increases in stress-related autonomic activation and higher levels of inflammation (see Hänsel et al., 2010 for review). In both samples, females were over-represented in the high arousal subgroups, which is consistent with increased rates of mood and anxiety disorders among women. Furthermore, both high arousal subgroups reported lower household incomes, suggesting that economic stress may also be a factor in greater stress-related autonomic arousal and inflammation. Despite differences in age between our high arousal subgroups and known associations between age and proinflammatory activity (Michaud et al., 2013), these groups did not show a detectable difference in inflammatory markers, or significant interactions between inflammatory markers and age. However, larger sample sizes may be necessary to detect such potential differences. Our results also suggest that perceived control did not detectably influence inflammatory marker levels, which may seem contrary to the pathological stress model. However, prior work has illustrated that perceived control may activate adaptive immune pathways that alter the effect of chronic stress and inflammation or the duration of acute inflammatory responses but not necessarily the magnitude of basal proinflammatory activity (Koolhaas et al., 2011; Ciavarra et al., 2018), suggesting perceived control may be impacting

outcomes through a separable mechanism. Unfortunately, we did not have data on adaptive immune markers, or multiple measurements of inflammatory markers in response to stress manipulations to test these potential hypotheses. This is an important area of future investigation.

4.2. Distinct affective symptom patterns across subgroups

Perceived control and subjective arousal also showed dissociable relationships with affective symptoms. Replicating across both samples, the high arousal and low control subgroup showed pathological elevations in depressive distress, anxious distress, and loss of interest relative to all other subgroups. The high arousal, high control subgroup showed less severe but still elevated symptoms of anxious distress and slight elevations in loss of interest in both samples. Both low control subgroups reported lower than average positive affect, consistent with prior work demonstrating a positive relationship between perceived control and levels of positive affect (Bogdan et al., 2012; MacAulay et al., 2014). In clinical samples, high negative affect symptoms (depression and anxiety), are often (on average) correlated with symptoms of anhedonia or fatigue. In our study, the two low control subgroups both showed low positive affect even though the low arousal, low control subgroup did not show comparable elevations in loss of interest, depressive or anxious distress relative to the sample mean and did not have co-occurring elevations in pro-inflammatory markers. This suggests a potentially unique effect of

low perceived control on limiting positive hedonic experiences, that is less dependent on pro-inflammatory mechanisms and stress. The lack of a detected relationship between perceived control and pro-inflammatory markers, and the unique effect of low perceived control on positive affect, offer further evidence regarding distinct mechanisms of action for perceived control and autonomic arousal as it relates to pathological affective outcomes and inflammation.

Some potential support for distinct mechanisms of action as stated above comes from the neurobehavioral literature. Bhanji and Delgado (2014) found that greater persistence following controllable setbacks correlated with reduced activity in the ventral striatum. Notably, reduced striatal response following controllable setbacks did not correlate with negative affect ratings or the intensity of setbacks, but altered behavior in the context of stress. However, when participants were led to believe that outcomes were uncontrollable, change in ventromedial prefrontal cortex (vmPFC) activity to setbacks, mediated the relationship between negative affect post setback and persistence (greater positive change associated with greater persistence). An interesting observation is that striatal activity driving individual differences in persistence following controllable setbacks is orthogonal to negative affect. Likewise, in the uncontrollable case, the mediating role of greater vmPFC activity is again to reduce the association between negative affect and persistence (see Stolz et al., 2020) for related findings). This suggests that the relative protective effect of perceived control observed in our high-arousal, high control subgroup may act through a similar mechanism, by allowing individuals to attribute positive outcomes to their own actions, engage in goal-oriented cognitions, and to dissociate the experience of adverse events, from what they might mean for future action/outcomes. However future experimentation is necessary to test these hypotheses.

Perceived control may also exert mental health-related benefits by influencing coping styles. For example, under conditions of high perceived control, stressors may increase motivation to engage in adaptive or healthy behaviors such as exercise or seeking social support. Conversely, those low in perceived control may be susceptible to coping efforts that sustain negative emotions when faced with stress or adversity (e.g. Burger, 1989; Fontaine et al., 1993), such as effortful avoidance or rumination (Lavender and Watkins, 2004; Dijkstra and Homan, 2016). Thus, control-linked styles of coping might be analogous to the long-standing distinction between problem and emotion-focused coping (Baker and Berenbaum, 2007), the latter of which has been associated with inflammatory disease (Jones et al., 2006; Iglesias-Rey et al., 2013) as well as the general severity of physical illness (Endler et al., 2001). Thus, future work evaluating the effects of personal control should also consider the potential moderating role of preferred coping strategies to further refine prediction of risk versus resilience toward the unfavorable health- and psychiatric-related consequences of stress and inflammation.

4.3. Limitations

As with any study, results presented here should be evaluated in light of study limitations. First, the cross-sectional and time-lagged nature of this study and data collection has obvious limitations with respect drawing causal conclusions about the findings. At the same time cross-sectional designs do have potential to investigate hypotheses that can be later tested in experimental designs. Relatedly, the current data allowed us to probe outcomes of naturally occurring stress/adversity in humans that could not be ethically manipulated in a lab setting. Another limitation stems from lack of direct control over the specific variables available and the unequal subgroup sample sizes. For example, while fully stratifying our sample by age, sex, and race, especially in the smaller subgroups, may have revealed additional nuance, doing so would have limited the power and interpretability of our results. We nevertheless attempted to test the sensitivity of our effect by including relevant covariates in our models and found that most key findings remained significant. Finally, self-reported measures of affective symptoms across positive and negative domains often correlate. These domains are often

also collinear with factor levels making them impossible to control statistically. Larger sample sizes that allow for stratification, or the use of other clinical comparison groups can improve our ability to dissociate these domains, if they are in fact dissociable. We attempted to address this potential issue of collinearity by choosing to separate individuals along hypothesized mechanistic dimensions of inflammation and affect rather than on the outcomes themselves (Elovainio et al., 2009; Dantzer et al., 2008).

We also acknowledge that despite large sample sizes reported effect sizes are relatively small. While not a direct limitation, we believe that this is due to several factors. First, larger samples generally result in smaller, but more reliable effect sizes, while smaller samples often result in higher but less reliable effect sizes. This is consistent with the replication of most of our results across both datasets. Second, our study did not focus on using clinical versus control samples. Had we done this, it would be expected that our effect sizes would be larger. Additionally, small effects sizes are consistent with findings reported in the literature, especially for pro-inflammatory markers (Howren et al., 2009). Studies reporting higher effect sizes have comparably smaller sample sizes and direct experimental manipulations of acute inflammation versus measures of basal inflammation (e.g. Kudinova et al., 2020).

4.4. Conclusions and future directions

Despite the limitations noted above, the current study provides initial evidence that while measures of autonomic arousal may allow for adequate dissociation of individual differences in high versus low inflammatory outcomes, individual differences in perceived control at both high and low subjective arousal are crucial for dissociating heterogeneity in clinically relevant affective outcomes. This may be especially true for identifying individual differences in hedonic capacity both with and without co-occurring negative affect, for making treatment decisions, and for better delineating resilient versus at-risk samples. One advantage of utilizing clustering approaches in large community and population-based samples, such as the one reported here, is improved identification of naturally occurring variability as it relates to hypothesized mechanistic phenotypes of affective and other health-related outcomes. As observed here, some of this variability is at low prevalence relative to the majority of the population (e.g., AA+/CNTL+ and AA+/CNTL-in the current study), which would inevitably mask effects at the total group level. Future work should extend findings from this study to experimentally or longitudinally test whether the phenotypic subgroups defined across arousal and perceived control dimensions in this study differ with respect behavioral or cognitive coping strategies, other health-related risks, or treatment response. Additional translational work should test the feasibility and efficacy of using basal inflammatory plus brief self-report measures of AA and CNTL in ambulatory settings to determine mental health risk and pathology.

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Declaration of competing interest

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Appendix A. Supplementary data

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References

Acabchuk, R.L., Kamath, J., Salamone, J.D., Johnson, B.T., 2017. Stress and chronic illness : the inflammatory pathway. Soc. Sci. Med. 185, 166–170. https://doi.org/10.1016/j.socscimed.2017.04.039.

Ambrée, O., Ruland, C., Scheu, S., Arolt, V., Alferink, J., 2018. Alterations of the innate immune system in susceptibility and resilience after social defeat stress. Front. Behav. Neurosci. 12 (July), 1–12. https://doi.org/10.3389/fnbeh.2018.00141.

Appelman, Y., van Rijn, B.B., ten Haaf, M.E., Boersma, E., Peters, S.A.E., 2014. Sex differences in cardiovascular risk factors and disease prevention. Atherosclerosis 241 (1), 211–218. https://doi.org/10.1016/j.atherosclerosis.2015.01.027.

Baker, J.P., Berenbaum, H., 2007. Emotional approach and problem-focused coping: a comparison of potentially adaptive strategies. Cognit. Emot. 21 (1), 95–118. https://doi.org/10.1080/02699930600562276.

Banasr, M., Dwyer, J.M., Duman, R.S., 2011. Cell atrophy and loss in depression: reversal by antidepressant treatment. Curr. Opin. Cell Biol. 23 (6), 730–737. https://doi.org/10.1016/j.ceb.2011.09.002.

Baron, R.M, Kenny, D.A., 1986. The Moderator-Mediator Variable Distinction in Social Psychological Research:Conceptual, Strategic, and Statistical Considerations. Journal of Personality and Social Psychology 51 (6), 1173–1182.

Bhanji, J.P., Delgado, M.R., 2014. Perceived control influences neural responses to setbacks and promotes persistence. Neuron 83 (6), 1369–1375. https://doi.org/10.1016/j.neuron.2014.08.012.

Bogdan, R., Pringle, P.L., Goetz, E.L., Pizzagalli, D.A., 2012. Perceived stress, anhedonia and illusion of control: evidence for two mediational models. Cognit. Ther. Res. 36 (6), 827–832. https://doi.org/10.1007/s10608-011-9413-8.

Bonilla-Jaime, H., Vázquez-Palacios, G., Arteaga-Silva, M., Retana-Márquez, S., 2006. Hormonal responses to different sexually related conditions in male rats. Hormones and Behavior 49, 376–382. https://doi.org/10.1016/j.yhbeh.2005.08.005.

Bronson, F.H., Desjardins, C., 1982. Endocrine responses to sexual arousal in male mice. Endocrinology 111 (4), 1286–1291. https://doi.org/10.1210/endo-111-4-1286.

Burger, J.M., 1989. Negative reactions to increases in perceived personal control. J. Pers. Soc. Psychol. 56 (2), 246–256.

Chobanyan-Jürgens, K., Jordan, J., 2015. Autonomic nervous system activity and inflammation: good ideas, good treatments, or both? Am. J. Physiol. Heart Circ. Physiol. 309 (12), H1999–H2001. https://doi.org/10.1152/ajpheart.00826.2015.

Ciavarra, R.P., Machida, M., Lundberg, P.S., Gauronskas, P., Wellman, L.L., Steel, C., Sanford, L.D., 2018. Controllable and uncontrollable stress differentially impact pathogenicity and survival in a mouse model of viral encephalitis. J. Neuroimmunol. 319 (May), 130–141. https://doi.org/10.1016/j.jneuroim.2018.02.014.

Clark, L.A., Watson, D., 1991. Tripartite model of anxiety and depression: psychometric eveidence and taxonomic implications. J. Abnorm. Psychol. 100 (3), 316–336. https://doi.org/10.1037/0021-843X.100.3.316.

Dang, R., Guo, Y.Y., Zhang, K., Jiang, P., Zhao, M.G., 2019. Predictable chronic mild stress promotes recovery from LPS-induced depression. Mol. Brain 12 (1), 1–12. https://doi.org/10.1186/s13041-019-0463-2.

Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci. https://doi.org/10.1038/nrn2297.

De Kloet, E.R., Joëls, M., Holsboer, F., 2005. Stress and the brain: from adaptation to disease. Nat. Rev. Neurosci. https://doi.org/10.1038/nrn1683.

Dickerson, S.S., Kemeny, M.E., 2004. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. Psychol. Bull. 130 (3), 355–391. https://doi.org/10.1037/0033-2909.130.3.355.

Dijkstra, M.T.M., Homan, A.C., 2016. Engaging in rather than disengaging from stress: effective coping and perceived control. Front. Psychol. 7 (SEP), 1–12. https://doi.org/10.3389/fpsyg.2016.01415.

Duivis, H.E., Vogelzangs, N., Kupper, N., De Jonge, P., Penninx, B.W.J.H., 2013. Differential association of somatic and cognitive symptoms of depression and anxiety with inflammation: findings from The Netherlands study of depression and anxiety (NESDA). Psychoneuroendocrinology. https://doi.org/10.1016/j.psyneuen.2013.01.002.

Elliot, A.J., Turiano, N.A., Infurna, F.J., Lachman, M.E., Chapman, B.P., 2018. Lifetime trauma, perceived control, and all-cause mortality: results from the Midlife in the United States Study. Health Psychol. 37 (3), 262–270. https://doi.org/10.1037/hea0000585.

Ellulu, M.S., Patimah, I., Khaza'ai, H., Rahmat, A., Abed, Y., 2017. Obesity and inflammation: the linking mechanism and the complications. Archives of Medical Science 13 (4), 851–863. https://doi.org/10.5114/aoms.2016.58928.

Elovainio, M., Aalto, A.M., Kivimäki, M., Pirkola, S., Sundvall, J., Lönnqvist, J., Reunanen, A., 2009. Depression and C-reactive protein: population-based health 2000 study. Psychosomatic Medicine. https://doi.org/10.1097/PSY.0b013e31819e333a.

Endler, N.S., Kocovski, N.L., Macrodimitris, S.D., 2001. Coping, efficacy, and perceived control in acute vs chronic illnesses. Pers. Indiv. Differ. 30 (4), 617–625. https://doi.org/10.1016/S0191-8869(00)00060-X.

Felger, J.C., Treadway, M.T., 2016. Inflammation effects on motivation and motor activity: role of dopamine. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology. https://doi.org/10.1038/npp.2016.143.

Foa, E.B., Zinbarg, R., Rothbaum, B.O., 1992. Uncontrollability and unpredictability in post-traumatic stress disorder: an animal model. Psychol. Bull. 112 (2), 218–238. https://doi.org/10.1037/0033-2909.112.2.218.

Fontaine, K.R., Manstead, A.S.R., Wagner, H., 1993. Optimism, perceived control over stress, and coping. Eur. J. Pers. 7 (4), 267–281. https://doi.org/10.1002/per.2410070407.

Glaser, R., Kiecolt-Glaser, J.K., 2005. Stress-induced immune dysfunction: implications for health. Nat. Rev. Immunol. https://doi.org/10.1038/nri1571.

Gülpinar, M.A., Özbeyli, D., Arbak, S., Yeğen, B.Ç., 2004. Anti-inflammatory effect of acute stress on experimental colitis is mediated by cholecystokinin-B receptors. Life Sci. 75 (1), 77–91. https://doi.org/10.1016/j.lfs.2003.12.009.

Hänsel, A., Hong, S., Cámara, R.J.A., von Känel, R., 2010. Inflammation as a psychophysiological biomarker in chronic psychosocial stress. Neurosci. Biobehav. Rev. 35 (1), 115–121. https://doi.org/10.1016/j.neubiorev.2009.12.012.

Hodes, G.E., Pfau, M.L., Leboeuf, M., Golden, S.A., Christoffel, D.J., Bregman, D., Russo, S.J., 2014. Individual differences in the peripheral immune system promote resilience versus susceptibility to social stress. Proc. Natl. Acad. Sci. Unit. States Am. 111 (45), 16136–16141. https://doi.org/10.1073/pnas.1415191111.

Howren, M.B., Lamkin, D.M., Suls, J., 2009. Associations of depression with c-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom. Med. 71 (2), 171–186. https://doi.org/10.1097/PSY.0b013e3181907c1b.

Iglesias-Rey, M., Barreiro-de Acosta, M., Caamaño-Isorna, F., Rodríguez, I.V., González, A.L., Lindkvist, B., Domínguez-Muñoz, E., 2013. How do psychological variables influence coping strategies in inflammatory bowel disease? Journal of Crohn's and Colitis 7 (6), e219–e226. https://doi.org/10.1016/j.crohns.2012.09.017.

Jänig, W., 2014. Sympathetic nervous system and inflammation: a conceptual view. Auton. Neurosci.: Basic and Clinical 182, 4–14. https://doi.org/10.1016/j.autneu.2014.01.004.

Jones, M.P., Wessinger, S., Crowell, M.D., 2006. Coping strategies and interpersonal support in patients with irritable bowel syndrome and inflammatory bowel disease. Clin. Gastroenterol. Hepatol. 4 (4), 474–481. https://doi.org/10.1016/j.cgh.2005.12.012.

Kaufman, L., Rousseeuw, P.J., 1990. Finding groups in data: an introduction to cluster Analysis (wiley series in probability and Statistics). Eepe.Ethz.Ch. https://doi.org/10.1007/s13398-014-0173-7.2.

Kenney, M.J., Ganta, C.K., 2014. Autonomic nervous system and immune system interactions. Comprehensive Physiology. https://doi.org/10.1002/cphy.c130051.

Kerr, D.L., McLaren, D.G., Mathy, R.M., Nitschke, J.B., 2012. Controllability modulates the anticipatory response in the human ventromedial prefrontal cortex. Front. Psychol. 3 (DEC), 1–11. https://doi.org/10.3389/fpsyg.2012.00557.

Kerschensteiner, M., Gallmeier, E., Behrens, L., Leal, V.V., Misgeld, T., Klinkert, W.E.F., Hohlfeld, R., 1999. Activated human T cells, B cells, and monocytes produce brain-derived neurotrophic factor in vitro and in inflammatory brain lesions: a neuroprotective role of inflammation? J. Exp. Med. 189 (5), 865–870. https://doi.org/10.1084/jem.189.5.865.

Koolhaas, J.M., De Boer, S.F., De Ruitter, A.J.H., Meerlo, P., Sgoifo, A., 1997. Social stress in rats and mice. Acta Physiol. Scand. Supplement.

Koolhaas, J.M.M., Bartolomucci, A., Buwalda, B., de Boer, S.F., Flügge, G., Korte, S.M.M., Fuchs, E., 2011. Stress revisited: a critical evaluation of the stress concept. Neurosci. Biobehav. Rev. 35 (5), 1291–1301. https://doi.org/10.1016/j.neubiorev.2011.02.003.

Kudinova, A.Y., Gano, A., James, K.M., Lawlor, C., Deak, T., Gibb, B.E., 2020. Anhedonia and increased evoked immune response. Brain, Behavior, & Immunity - Health 6 (June), 100090. https://doi.org/10.1016/j.bbih.2020.100090.

Kunz-Ebrecht, S.R., Mohamed-Ali, V., Feldman, P.J., Kirschbaum, C., Steptoe, A., 2003. Cortisol responses to mild psychological stress are inversely associated with proinflammatory cytokines. Brain Behav. Immun. 17 (5), 373–383. https://doi.org/10.1016/S0889-1591(03)00029-1.

Lachman, M.E., Weaver, S.L., 1998. The Sense of Control as a Moderator of Social Class Differences in Health and Well-Being, vol. 74, pp. 763–773, 3.

Larson, C.L., Nitschke, J.B., Davidson, R.J., 2007. Common and distinct patterns of affective response in dimensions of anxiety and depression. Emotion 7 (1), 182–191. https://doi.org/10.1037/1528-3542.7.1.182.

Lavender, A., Watkins, E., 2004. Rumination and future thinking in depression. Br. J. Clin. Psychol. 43 (2), 129–142. https://doi.org/10.1348/014466504323088015.

Legault, L., Al-Khindi, T., Inzlicht, M., 2012. Preserving integrity in the face of performance threat: self-affirmation enhances neurophysiological responsiveness to errors. Psychol. Sci. 23 (12), 1455–1460. https://doi.org/10.1177/0956797612448483.

Lewitus, G.M., Schwartz, M., 2009. Behavioral immunization: immunity to self-antigens contributes to psychological stress resilience. Mol. Psychiatr. 14 (5), 532–536. https://doi.org/10.1038/mp.2008.103.

MacAulay, R.K., McGovern, J.E., Cohen, A.S., 2014. Understanding anhedonia: the role of perceived control. In: Ritsner, M.S. (Ed.), Anhedonia: A Comprehensive Handbook Volume I, vol. I. Springer, pp. 23–40. https://doi.org/10.1007/978-94-017-8610-2.

Maier, S.U., Makwana, A.B., Hare, T.A., 2015. Acute stress impairs self-control in goal-directed choice by altering multiple functional connections within the brain's decision circuits. Neuron 87 (3), 622–632. https://doi.org/10.1016/j.neuron.2015.07.005.

Martins-De-Souza, D., Maccarrone, G., Ising, M., Kloiber, S., Lucae, S., Holsboer, F., Turck, C.W., 2014. Plasma fibrinogen: now also an antidepressant response marker? Transl. Psychiatry 4 (1), e352–e354. https://doi.org/10.1038/tp.2013.129.

McEwen, B.S., Wingfield, J.C., 2003. The concept of allostasis in biology and biomedicine. Horm. Behav. https://doi.org/10.1016/S0018-506X(02)00024-7.

Michaud, M., Balardy, L., Moulis, G., Gaudin, C., Peyrot, C., Vellas, B., Nourhashemi, F., 2013. Proinflammatory cytokines, aging, and age-related diseases. J. Am. Med. Dir. Assoc. 14 (12), 877–882. https://doi.org/10.1016/j.jamda.2013.05.009.

Michopoulos, V., Jovanovic, T., 2015. Chronic inflammation: a new therapeutic target for post-traumatic stress disorder? The Lancet Psychiatry. https://doi.org/10.1016/S2215-0366(15)00355-7.

Miller, A.H., Haroon, E., Raison, C.L., Felger, J.C., 2013. Cytokine targets in the brain: impact on neurotransmitters and neurocircuits. Depress. Anxiety 30 (4), 297–306. https://doi.org/10.1002/da.22084.

Miller, A.H., Raison, C.L., 2015. Are anti-inflammatory therapies viable treatments for psychiatric disorders? Where the rubber meets the road. JAMA Psychiatry 72 (6), 527–528. https://doi.org/10.1001/jamapsychiatry.2015.22.

Miller, A.H., Raison, C.L., 2016. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat. Rev. Immunol. 16 (1), 22–34. https://doi.org/10.1038/nri.2015.5.

Miller, G.A., Chapman, J.P., 2001. Misunderstanding analysis of covariance. J. Abnorm. Psychol. https://doi.org/10.1037/0021-843X.110.1.40.

Moller, A.C., Deci, E.L., Ryan, R.M., 2006. Choice and ego-depletion: the moderating role of autonomy. Pers. Soc. Psychol. Bull. 32 (8), 1024–1036. https://doi.org/10.1177/0146167206288008.

O'Donovan, A., Hughes, B.M., Slavich, G.M., Lynch, L., Cronin, M.T., O'Farrelly, C., Malone, K.M., 2010. Clinical anxiety, cortisol and interleukin-6: evidence for specificity in emotion-biology relationships. Brain Behav. Immun. 24 (7), 1074–1077. https://doi.org/10.1016/j.bbi.2010.03.003.

Patall, E.A., Cooper, H., Robinson, J.C., 2008. The effects of choice on intrinsic motivation and related outcomes: a meta-analysis of research findings. Psychol. Bull. 134 (2), 270–300. https://doi.org/10.1037/0033-2909.134.2.270.

Pfau, M.L., Russo, S.J., 2015. Peripheral and central mechanisms of stress resilience. Neurobiology of Stress 1 (1), 66–79. https://doi.org/10.1016/j.ynstr.2014.09.004.

Pongratz, G., Straub, R.H., 2014. The Sympathetic Nervous Response in Inflammation. Retrieved from. http://arthritis-research.com/content/16/6/504.

Radler, B., 2014. The Midlife in the United States (MIDUS) Series: A National Longitudinal Study of Health and Well-being. Open Health Data 2 (1), 1–7. https://doi.org/10.5334/ohd.ai.

Reeve, J., Nix, G., Hamm, D., 2003. Testing models of the experience of self-determination in intrinsic motivation and the conundrum of choice. J. Educ. Psychol. 95 (2), 375–392. https://doi.org/10.1037/0022-0663.95.2.375.

Scheller, J., Chalaris, A., Schmidt-Arras, D., Rose-John, S., 2011. The pro- and anti-inflammatory properties of the cytokine interleukin-6. Biochim. Biophys. Acta Mol. Cell Res. 1813 (5), 878–888. https://doi.org/10.1016/j.bbamcr.2011.01.034.

Schmidt, M., Naumann, H., Weidler, C., Schellenberg, M., Anders, S., Straub, R.H., 2006. Inflammation and sex hormone metabolism. Ann. N. Y. Acad. Sci. 1069, 236–246. https://doi.org/10.1196/annals.1351.021.

Schneider, B.A., Avivi-Reich, M., Mozuraitis, M., 2015. A cautionary note on the use of the Analysis of Covariance (ANCOVA) in classification designs with and without within-subject factors. Front. Psychol. https://doi.org/10.3389/fpsyg.2015.00474.

Simons, R.L., Lei, M.K., Beach, S.R.H., Barr, A.B., Cutrona, C.E., Gibbons, F.X., Philibert, R.A., 2017. An index of the ratio of inflammatory to antiviral cell types mediates the effects of social adversity and age on chronic illness. Soc. Sci. Med. 185, 158–165. https://doi.org/10.1016/j.socscimed.2017.03.005.

Steptoe, A., Hamer, M., Chida, Y., 2007. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. Brain Behav. Immun. https://doi.org/10.1016/j.bbi.2007.03.011.

Stolz, D.S., Müller-Pinzler, L., Krach, S., Paulus, F.M., 2020. Internal control beliefs shape positive affect and associated neural dynamics during outcome valuation. Nat. Commun. 11 (1), 1–13. https://doi.org/10.1038/s41467-020-14800-4.

Taylor, C.B., 2010. Depression, heart rate related variables and cardiovascular disease. Int. J. Psychophysiol. https://doi.org/10.1016/j.ijpsycho.2010.04.006.

Wirth, M.M., Schultheiss, O.C., 2006. Effects of affiliation arousal (hope of closeness) and affiliation stress (fear of rejection) on progesterone and cortisol. Horm. Behav. 50 (5), 786–795. https://doi.org/10.1016/j.yhbeh.2006.08.003.

Wium-Andersen, M.K., Ørsted, D.D., Nordestgaard, B.G., 2013. Elevated plasma fibrinogen, psychological distress, antidepressant use, and hospitalization with depression: two large population-based studies. Psychoneuroendocrinology 38 (5), 638–647. https://doi.org/10.1016/j.psyneuen.2012.08.006.

Won, E., Kim, Y.-K., 2016. Stress, the autonomic nervous system, and the immune-kynurenine pathway in the etiology of depression. Curr. Neuropharmacol. 14 (7), 665–673. https://doi.org/10.2174/1570159X14666151208113006.

Yang, C., Shirayama, Y., Zhang, J.C., Ren, Q., Hashimoto, K., 2015. Regional differences in brain-derived neurotrophic factor levels and dendritic spine density confer resilience to inescapable stress. Int. J. Neuropsychopharmacol. 18 (7), 1–6. https://doi.org/10.1093/ijnp/pyu121.