

Neural sensitivity to social rejection is associated with inflammatory responses to social stress

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Contributed by Shelley E. Taylor, June 25, 2010 (sent for review April 21, 2010)

Although stress-induced increases in inflammation have been implicated in several major disorders, including cardiovascular disease and depression, the neurocognitive pathways that underlie inflammatory responses to stress remain largely unknown. To examine these processes, we recruited 124 healthy young adult participants to complete a laboratory-based social stressor while markers of inflammatory activity were obtained from oral fluids. A subset of participants ($n = 31$) later completed an fMRI session in which their neural responses to social rejection were assessed. As predicted, exposure to the laboratory-based social stressor was associated with significant increases in two markers of inflammatory activity, namely a soluble receptor for tumor necrosis factor- α (sTNF α RII) and interleukin-6 (IL-6). In the neuroimaging subsample, greater increases in sTNF α RII (but not IL-6) were associated with greater activity in the dorsal anterior cingulate cortex and anterior insula, brain regions that have previously been associated with processing rejection-related distress and negative affect. These data thus elucidate a neurocognitive pathway that may be involved in potentiated inflammatory responses to acute social stress. As such, they have implications for understanding how social stressors may promote susceptibility to diseases with an inflammatory component.

anterior cingulate | insula | inflammation | depression | disease

Psychological stress is intimately related to human health and well-being. It increases susceptibility to the common cold (1), elevates risk for several major diseases (2), and is a strong, independent predictor of morbidity and mortality. In a recent epidemiological study, for example, males experiencing high levels of stress were 32% more likely to die during a 22-y assessment period than were those experiencing low levels of stress (3).

Stress may affect health in part by up-regulating inflammatory processes that have been implicated in the onset or progression of several disorders, including asthma, rheumatoid arthritis, cardiovascular disease, and depression (4–8). Although many stressors can have this effect, animal and human research has shown that social stressors are particularly strong triggers of inflammation (9–11). Exposure to everyday social stress in humans, for example, is associated with elevated inflammatory activity (12–15) and with the up-regulated expression of genes that promote inflammation (16). In addition, controlled laboratory studies have shown that acute social stressors—specifically ones that involve social evaluation and the possibility of social rejection—elicit significant increases in proinflammatory cytokines, a key mediator of the inflammatory response (17, 18).

Despite evidence that social stressors may trigger inflammation, the neurocognitive pathways that underlie this effect remain unknown. In particular, no studies to date have investigated the neural regions associated with differences in inflammatory responding to acute social stress. The brain plays a critical role in appraising social stressors, as well as in modulating the immune system's response to stressors that involve social or physical threat (19–21). Differences in inflammatory responses to social stress may thus be explained, at least in part, by individual differences in activity in neural regions that process social threat-related information.

Insofar as stressors involving the possibility of social rejection up-regulate inflammatory activity (17, 18), neural regions involved

in processing rejection-related distress may relate to individuals' magnitude of inflammatory responses to social stress. On the basis of prior research, these brain regions include the dorsal anterior cingulate cortex (dACC) and the anterior insula. Exposure to an acute episode of social rejection or to rejection-related cues has been shown to activate both the dACC and the anterior insula (22, 23); greater activity in the dACC, in turn, has been associated with greater self-reported feelings of social distress (e.g., "I felt rejected") (22, 24). Exposure to social-evaluative threat also has been shown to activate the dACC (25). Thus, neural regions associated with social rejection-related distress may play a role in inflammatory responses to stressors that involve elements of social-evaluative threat and rejection.

To examine whether neural regions involved in processing rejection-related information are associated with inflammatory responses to an episode of acute social stress, we administered two tasks to a sample of healthy young adult participants. First, we exposed participants ($n = 124$) to a laboratory-based social stressor, the Trier Social Stress Test (TSST) (26), which involves preparing and delivering an impromptu speech and performing difficult mental arithmetic in front of a nonresponsive, socially rejecting panel of raters. To quantify the magnitude of participants' inflammatory response to this stressor, we collected oral fluids during the stressor and assessed two key markers of inflammatory activity—namely, a soluble receptor for tumor necrosis factor- α (sTNF α RII) and interleukin-6 (IL-6). In a subsequent session, a subset of these participants ($n = 31$) was scanned while they played a computerized ball-tossing game called "Cyberball" (27), in which participants were ultimately excluded by two other supposed players, leading to an experience of social rejection. We then examined how differences in neural activity during social rejection correlated with differences in inflammatory responses to the TSST. On the basis of prior research, we made two predictions. First, we hypothesized that the TSST would elicit significant increases in inflammatory activity. Second, we hypothesized that greater inflammatory responses to the TSST would be associated with greater neural activity in the dACC and anterior insula during social rejection.

Results

Inflammatory Responses to Acute Social Stress. As predicted, exposure to the TSST elicited significant increases (from baseline to post-TSST) in levels of both sTNF α RII, $F(1, 123) = 9.78, P < 0.005, \eta^2 = 0.074$, and IL-6, $F(1, 123) = 4.39, P < 0.05, \eta^2 = 0.034$ (see Fig. 1). These effects did not differ as a function of gender, ethnicity, or body mass index (BMI) (all P s > 0.17). Changes in sTNF α RII and IL-6 were positively correlated, $r = 0.53, P < 0.001$. Thus, exposure to the TSST, which involves elements of

Author contributions: G.M.S., B.M.W., N.I.E., and S.E.T. designed research; G.M.S., B.M.W., N.I.E., and S.E.T. performed research; G.M.S., B.M.W., and N.I.E. analyzed data; and G.M.S., B.M.W., N.I.E., and S.E.T. wrote the paper.

The authors declare no conflict of interest.

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This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1009164107/-DCSupplemental.

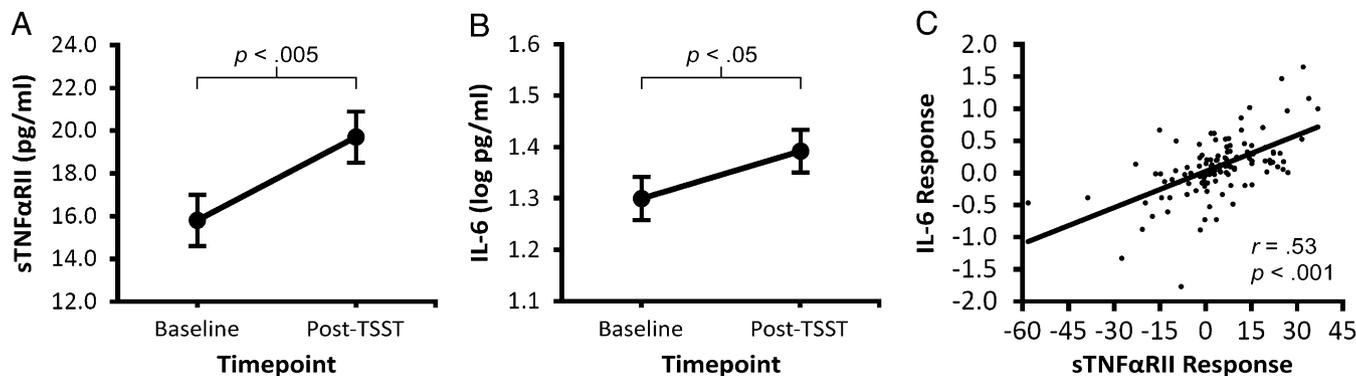


Fig. 1. Levels of the inflammatory markers. Shown are (A) a soluble receptor for tumor necrosis factor- α (sTNF α RII) and (B) interleukin-6 (IL-6) at baseline (Baseline) and following exposure to the Trier Social Stress Test (Post-TSST), expressed as mean \pm SEM. The TSST elicited significant increases in both sTNF α RII and IL-6. (C) The relation between sTNF α RII and IL-6 responses to the TSST, where response is calculated as post-TSST minus baseline ($n = 124$).

social-evaluative threat and rejection, triggered significant increases in inflammatory activity.

Neural Correlates of Inflammatory Responses to Acute Social Stress.

Next, we examined participants who had been scanned while they played Cyberball ($n = 31$) to test associations between their neural responses to social rejection and their inflammatory responses to acute social stress. As with the full sample, exposure to the TSST in this neuroimaging subsample elicited significant increases in both sTNF α RII, $F(1, 30) = 12.58$, $P < 0.001$, $\eta^2 = 0.30$, and IL-6, $F(1, 30) = 12.36$, $P < 0.001$, $\eta^2 = 0.29$. These effects did not differ by gender, ethnicity, or BMI (all P s > 0.1). In addition, changes in levels of sTNF α RII and IL-6 were again significantly and positively correlated, $r = 0.53$, $P < 0.005$.

To examine the hypothesis that greater inflammatory responses to the TSST would be associated with greater neural responses to social rejection, we used a region of interest (ROI)-based approach that involved selecting the dACC and anterior insula as a priori anatomical ROIs. Activity in these brain regions during social exclusion (vs. inclusion) was unrelated to baseline levels of sTNF α RII and IL-6 (all P s > 0.1). Consistent with hypotheses, however, greater increases in sTNF α RII in response to the TSST were significantly associated with greater activity in the dACC ROI ($r = 0.48$, $P < 0.005$), left anterior insula ROI ($r = 0.34$, $P < 0.05$), and right anterior insula ROI ($r = 0.30$, $P < 0.05$; see Fig. 2). Changes in IL-6 were unrelated to activity in the dACC and left anterior insula ROIs (P s > 0.2), but were marginally related to activity in the right anterior insula ROI ($r = 0.26$, $P = 0.08$).

To more fully explore these effects, we supplemented the anatomical ROI analyses with whole-brain regression analyses to examine which neural regions were associated with sTNF α RII and IL-6 responses to the TSST ($P < 0.001$, 20-voxel extent threshold). Consistent with the ROI analyses, and as shown in Table 1, greater TSST-induced increases in sTNF α RII were associated with greater activity in the dACC ($r = 0.67$, $P < 0.001$; see Fig. 3) and left anterior insula ($r = 0.63$, $P < 0.001$) during social exclusion (vs. inclusion), as well as with several other areas in the cortex, midbrain, and cerebellum. IL-6 was unrelated to activations in higher cortical, paralimbic, or limbic areas (Table S1). Finally, no brain regions were negatively correlated with changes in sTNF α RII or IL-6.

Discussion

The present study demonstrates that a social stressor involving social-evaluative threat and rejection elicits significant increases in inflammatory activity, as indexed by both sTNF α RII and IL-6 (see also refs. 17 and 18). To examine the neurocognitive pathways that might underlie this effect, we focused on brain regions previously implicated in processing rejection-related distress and negative affect. Anatomical ROI analyses revealed that greater

activity in the dACC and bilateral anterior insula during social exclusion (vs. inclusion) was associated with greater sTNF α RII responses to the laboratory-based social stressor; greater activity in the right anterior insula was marginally related to increases in IL-6.

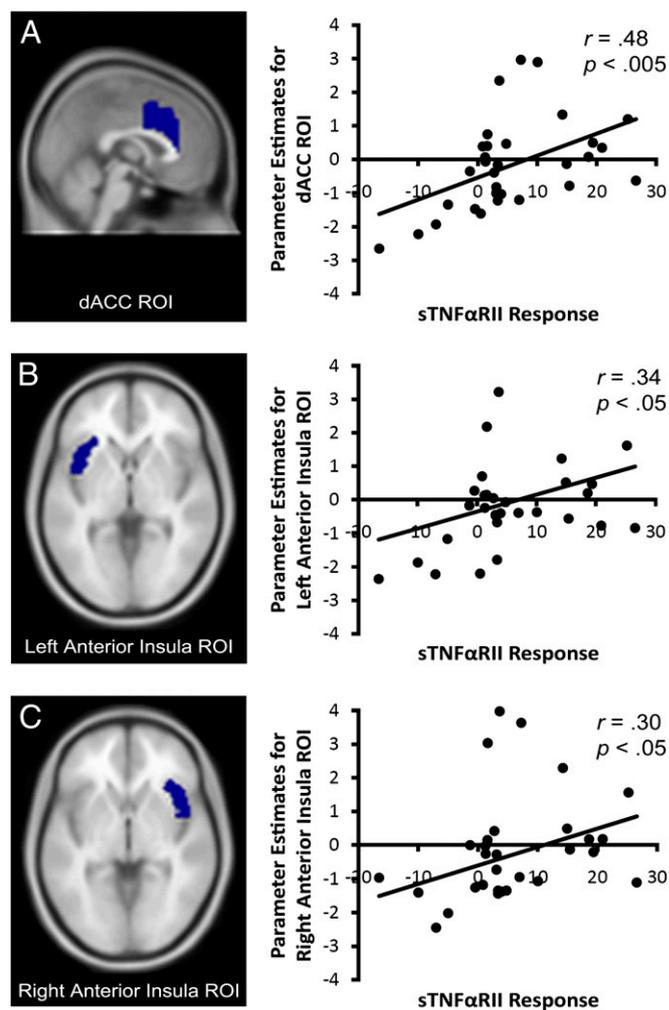


Fig. 2. Relations between inflammatory responses to the Trier Social Stress Test (TSST), as indexed by changes in levels of a soluble receptor for tumor necrosis factor- α (sTNF α RII), and activity in the (A) dorsal anterior cingulate cortex (dACC) ROI, (B) left anterior insula ROI, and (C) right anterior insula ROI. Greater activity in these brain regions during social exclusion (vs. inclusion) was significantly associated with greater sTNF α RII responses to the TSST ($n = 31$).

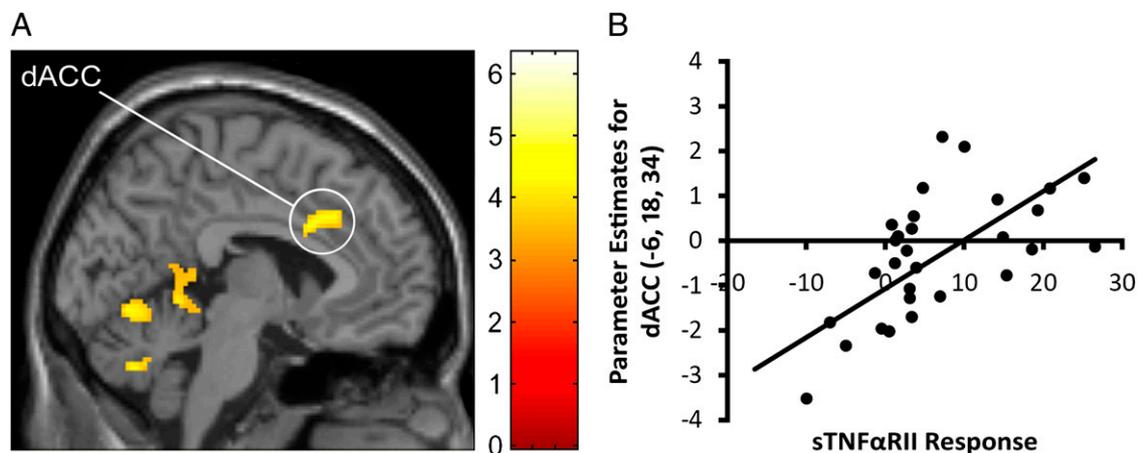


Fig. 3. (A) Neural activity in the dorsal anterior cingulate cortex (dACC) during social exclusion (vs. inclusion) that correlated positively with inflammatory responses to the Trier Social Stress Test (TSST), as indexed by changes in levels of a soluble receptor for tumor necrosis factor- α (sTNF α RII). (B) Scatterplot showing the relation between mean activity in the dACC cluster (thresholded at $P < 0.001$, 20 voxels) and sTNF α RII responses to the TSST. Greater activity in the dACC was significantly associated with greater sTNF α RII responses to the TSST ($n = 31$).

These associations were consistent with whole-brain analyses, which confirmed that greater activity in the dACC and left anterior insula was associated with greater increases in sTNF α RII. Considered together, these data demonstrate that neural responses to social rejection are associated with potentiated inflammatory responses to an episode of acute social stress.

Interestingly, the relations between neural activity and inflammatory responding were found despite the fact that the neu-

roimaging session and social stressor session took place several weeks apart. This result suggests that these neural patterns of responding represent at least a moderately stable trait that, in turn, is involved in potentiated inflammatory responses to social stress. Consistent with this formulation, greater social rejection-induced dACC activity during an fMRI session has been associated with greater self-reported distress during daily social interactions (28). Moreover, there is considerable evidence that individual differ-

Table 1. Neural activity during social exclusion (vs. inclusion) that was significantly associated with greater inflammatory responses to the Trier Social Stress Test (TSST), as indexed by changes in levels of a soluble receptor for tumor necrosis factor- α (sTNF α RII) ($n = 31$)

Brain region	Brodmann area	MNI coordinates	Cluster size (k)	t	r (TNF)
Paralimbic					
dACC	BA 24	-6 18 34	351	4.58	0.67
dACC	BA 24	12 38 0	29	4.45	0.63
Anterior insula		-34 -22 28	45	4.44	0.63
Parahippocampal gyrus	BA 36	-22 -20 -30	31	4.13	0.60
Cortex					
Middle frontal gyrus	BA 10/46	-30 52 12	99	4.54	0.64
Inferior frontal gyrus	BA 45	50 26 20	23	3.80	0.59
Precuneus	BA 30	4 -46 -4	454	6.08	0.71
Fusiform gyrus	BA 37	-40 -60 -12	28	4.41	0.63
Lingual gyrus	BA 18	26 -74 0	296	6.33	0.71
Lingual gyrus	BA 18	-4 -70 -8	107	4.36	0.63
Fusiform gyrus	BA 18	22 -98 -10	21	3.75	0.58
Subcortical and cerebellum					
Caudate		18 18 14	79	4.34	0.61
Thalamus		-20 -28 14	51	4.30	0.62
Midbrain (substantia nigra)		-12 -12 -12	20	4.16	0.62
Medulla		6 -32 -48	30	4.09	0.61
Cerebellum		32 -48 -36	49	4.41	0.64
Cerebellum		-4 -70 -34	35	4.23	0.62
Cerebellum		-28 -44 -24	21	4.05	0.60
Cerebellum		-22 -72 -34	45	4.00	0.59

The brain regions listed represent those that were significantly related to TSST-induced changes in sTNF α RII, thresholded at $P < 0.001$, 20 voxels. dACC is the dorsal anterior cingulate cortex; BA refers to putative Brodmann's area; MNI coordinates identify the local maxima of particular brain activations, reported in Montreal Neurological Institute (MNI) format; Cluster size (k) is the number of voxels in each activation cluster that was significantly associated with greater sTNF α RII responses to the TSST; t is the t -value at those coordinates (local maxima); r (TNF) is the correlation coefficient describing the strength of association between the activation cluster and sTNF α RII response to the TSST.

ences in inflammatory responses to stress are relatively stable over time (29, 30).

It is also important to note that although dACC and bilateral anterior insula activity was significantly related to sTNF α RII, IL-6 was related only to right anterior insula activity ($P = 0.08$). At least three explanations are possible. First, variability in TSST-induced inflammatory responses was substantially greater for sTNF α RII (SD = 11.03) than for IL-6 (SD = 3.02), making it easier to detect associations for sTNF α RII. Second, because TNF responses occur earlier in the inflammatory cascade, our assessment time points may have been more appropriate for capturing TSST-induced changes in sTNF α RII. Finally, the dACC and anterior insula may simply not be directly involved in IL-6 responses to acute social stress.

One critical question raised by the present findings concerns *why* neural sensitivity to social rejection would relate to inflammatory responding. There are several possible reasons. First, to the extent that physical threats are more likely to occur in situations that involve social threat or rejection, social rejection may trigger inflammatory activity to manage the possibility of injury. Inflammatory cytokines are released in response to impending (or actual) physical assault because they can accelerate wound healing and reduce risk for infection (10, 17). Cytokines also induce a constellation of behaviors called *sickness behaviors*, which promote recuperation, limit transmission of pathogens to others, and reduce risk for additional conflict (10, 31). Neural regions that process rejection-related information may thus be involved in inflammatory responding because they help organisms mount preparatory responses to potential physical injury. A second reason for why neural responses to social rejection might relate to inflammatory responding is based on overlapping neural circuitry underlying physical and social pain (22). To the extent that physical pain (or the possibility of physical pain) triggers inflammatory responding to manage physical injury, social rejection may be capable of triggering these processes as well because it utilizes some of the same pain-related neural systems.

A second question raised by these findings concerns *how* the dACC and anterior insula are involved in generating inflammatory responses to stress. Relevant to this issue is a growing body of research suggesting that the ACC and anterior insula function as an integrated circuit (32, 33), forming a key node in the visceromotor network (34). Both regions appear to be involved in high-level representation of visceral states (35), which may include neural encoding of peripheral inflammation (36–38), and they are connected to the periphery in several ways that give these paralimbic structures the ability to modulate inflammatory activity. For example, both the ACC and the anterior insula have extensive efferent connections to the hypothalamus (39), enabling them to influence inflammatory activity via endocrine pathways. In addition, these regions project to the brainstem autonomic control nuclei (40), where peripheral inflammatory processes can be regulated by sympathetic and parasympathetic activity (20).

Although we did not assess health outcomes in the present study, it is possible that individual differences in magnitude of inflammatory responses to social stress may have implications for health (41). Specifically, they may help to explain the considerable variability that has been observed in susceptibility to disorders with an inflammatory component, including asthma (4), arthritis (5), cardiovascular disease (6), certain types of cancer (7), and depression (8). Risk for depression, for example, increases substantially following rejection-related life events (42, 43), but not all people who experience rejection become depressed. Greater neural responses to rejection may be associated with greater inflammatory activity, which is subsequently reflected in the pathogenesis of inflammatory-related disorders such as depression (44).

A limitation of the present study is that the associations observed between neural activity and inflammatory responding were correlational and, as such, causality cannot be determined. Furthermore,

additional research is needed to examine whether neural responses to social rejection are uniquely related to differences in inflammatory responding or, alternatively, whether they are part of a more general “stress” system that can be activated by several types of negative events that also relate to inflammatory responding. Nevertheless, across several studies and different sets of emotional stimuli, the dACC and anterior insula are the primary sites of neural activation that correlate with stress-related physiological responding (see refs. 24, 25, and 45–47). The emerging neurocognitive account, therefore, is that brain regions involved in processing social rejection-related information are associated with a variety of biological responses to social and physical threat. These brain regions may thus have important implications for health in general and susceptibility to inflammatory diseases in particular.

Materials and Methods

Participants. Advertisements for a study of psychological responses to stress were posted on the University of California, Los Angeles (UCLA) campus. Respondents were screened to recruit those in good physical and mental health. Prospective participants were excluded if they had a diagnosed physical or mental health problem; were experiencing a cold, viral infection, or other inflammatory condition (e.g., asthma, bronchitis, thyroid problems, gingivitis, etc.); were exhibiting symptoms consistent with a cold or infection (e.g., sore throat, runny nose, sweating, coughing, bleeding gums, etc.); were taking psychiatric medications or medications affecting cardiovascular or endocrine function; were seeing a mental health professional; or were pregnant or breastfeeding. One hundred twenty-four individuals (54 males, 70 females) met these criteria and received \$60 for participating in the laboratory social stressor component of the study. These participants ranged in age from 18 to 36 ($M = 21.25$, $SD = 2.62$; males, $M = 21.40$, $SD = 3.36$; females, $M = 21.13$, $SD = 1.88$) and were ethnically diverse (i.e., 34.7% Asian American, 34.7% European American, 11.3% Hispanic/Latino, 7.3% Middle Eastern, 4.0% African American, and 8.0% “mixed” or other).

Participants from this sample were subsequently invited to participate in a neuroimaging study. Respondents were screened to determine if they met the fMRI-related inclusion criteria of being right-handed, not claustrophobic, and free of bodily metals (except dental fillings, which were allowed) or other conditions that could have prevented them from being scanned (e.g., pacemaker). Thirty-three individuals met these criteria and received an additional \$20 for their time. Data for one individual was unusable as an extreme outlier (i.e., >3 SDs below the mean on neural activity) and another individual had been previously administered the Cyberball task; as a result, they were omitted from the MRI analyses. The final neuroimaging subsample thus consisted of 31 participants (12 males, 19 females) who ranged in age from 18 to 36 ($M = 21.30$, $SD = 3.10$; males, $M = 22.17$, $SD = 4.57$; females, $M = 20.72$, $SD = 1.41$). The ethnic diversity of this subsample was representative of the larger sample (i.e., 35.5% Asian American, 25.8% European American, 16.1% Hispanic/Latino, 6.5% Middle Eastern, 6.5% African American, and 9.6% mixed or other). All participants provided written informed consent and all procedures were preapproved by the UCLA Institutional Review Board. The present report associates the neuroimaging and TSST-related inflammatory data for these participants.

Laboratory Social Stressor Paradigm. Laboratory social stressor sessions were scheduled between 2:30 and 4:30 PM to minimize variability due to diurnal variation in inflammatory activity and cortisol production (48, 49). Participants were told to not eat, exercise, or consume caffeine for at least 1 h before their session.

Information about participants’ social and interpersonal functioning (not part of the present study) was collected upon arrival. Participants were then escorted into the laboratory for the TSST, a widely used laboratory stress task that has been shown to up-regulate inflammatory activity (10, 11). Following a baseline rest period of 10 min, participants were asked to prepare (5 min) and deliver (5 min) a speech on why they would be a good administrative assistant. The speech was delivered to an unresponsive, socially rejecting panel of two raters who behaved nonverbally as if they found the speech to be lacking in quality. Participants were then asked to complete difficult mental arithmetic out loud (5 min). Specifically, they were asked to start at 2,935 and to count backward by 7’s and by 13’s while being urged to go faster by an apparently exasperated experimenter. These tasks were followed by a 30-min recovery period, during which time participants completed a packet of questionnaires (not part of the present study).

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