Running Head: BETA-BLOCKADE AND STRESS

Beta-adrenergic contributions to emotion and physiology during an acute psychosocial stressor

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Abstract

Objective: Beta-adrenergic receptor signaling, a critical mediator of sympathetic nervous system influences on physiology and behavior, has long been proposed as one contributor to subjective stress. Yet prior findings are surprisingly mixed about whether beta-blockade (e.g., propranolol) blunts subjective stress, with many studies reporting no effects. We re-evaluated this question in the context of an acute psychosocial stressor with more comprehensive measures and a larger-than-typical sample. We also examined the effects of beta-blockade on psychophysiological indicators of sympathetic and parasympathetic nervous system reactivity, given that beta-blockade effects for these measures specifically under acute psychosocial stress are not yet well-established.

Methods: In a double-blind, randomized, placebo-controlled study, 90 healthy young adults received 40 mg of the beta-blocker propranolol or placebo. Participants then completed the Trier Social Stress Test, which involved completing an impromptu speech and difficult arithmetic in front of evaluative judges. Self-reported emotions and appraisals as well as psychophysiology were assessed throughout.

Results: As expected, propranolol blunted TSST pre-ejection period reactivity (b=9.68, p=.003), a marker of sympathetic nervous system activity, as well as salivary alpha amylase reactivity (b=-.50, p=.006). Critically, propranolol also blunted negative, high arousal emotions in response to the stressor (b=-.22, p=.026), but cognitive appraisals remained intact (bs<-.17, ps>.10).

Conclusions: These results provide updated experimental evidence that beta-adrenergic signaling contributes to negative, high arousal emotions in response to a psychosocial stressor while also blunting sympathetic nervous system reactivity. Together, these findings shed light on the neurophysiological mechanisms by which stressors transform into the subjective experience we call "stress."

Trial Registration: NCT02972554

Keywords: Emotion, Appraisals, Stress, Beta-Blockade, Propranolol, Psychophysiology

Acronyms*:* BMI = body mass index*;* HPA axis = hypothalamic-pituitary-adrenal axis; HR = heart rate*;* PEP = pre-ejection period*;* PNS = parasympathetic nervous system*;* RSA = respiratory sinus arrhythmia*;* sAA = salivary alpha-amylase; SNS = sympathetic nervous system*;* TSST= Trier Social Stress Test

Psychological stressors have long been appreciated as determinants of physical health, emotional well-being, and social behavior (1–5). Importantly, subjective stress—the affective feelings and appraisals that individuals experience in the face of a stressor—is sometimes more predictive of health and wellbeing than "objective" measures such as cardiovascular or neuroendocrine markers (5–8). Despite the predictive utility of subjective stress, we know surprisingly little about how subjective stress is generated in the first place. Some work has tested potential neurophysiological contributions to subjective stress in humans by administering beta-blockers such as *propranolol*, which block beta-adrenergic receptors, a critical signaling pathway for epinephrine and norepinephrine (9,10). This study aimed to provide a more complete understanding of the effects of beta-blockade on the acute stress experience while also shedding light on longstanding questions about the nature of human emotion.

Current neuroscientific perspectives argue that the brain's core function is *allostasis*, the process of monitoring, managing, and coordinating physiology to support an organism's movement, growth, reproduction, and behavior (11,12). Two closely interworking systems by which the brain may in part enact allostasis are the sympathetic nervous system (SNS) and adrenergic/noradrenergic systems. These systems are known to support arousal and the mobilization of neurophysiological resources underpinning alertness, saliency, and behavioral coping (13–15). In particular, the catecholamines epinephrine and norepinephrine are released by the medulla in the adrenal glands and by the ends of sympathetic nerve fibers, serving as the primary neurotransmitters that convey SNS signaling to peripheral organs (16). Epinephrine and norepinephrine subsequently act by binding to alpha- and beta-adrenergic receptors, found widely across the body and brain (17,18).

Beta-adrenergic receptor signaling has long been implicated in the generation of affect (e.g., feeling tense, stressed, anxious), given its role in conveying epinephrine- and norepinephrine-mediated SNS signals to peripheral organs. The idea that peripheral signals contribute to affect is consistent with early theories of emotion (19,20) as well as current theories arguing that both the body's physiological states and interoception of those states help generate *affect*, or feelings of valence (pleasure vs. displeasure) and arousal (activation vs. quiescence; (21,22)). To test these ideas, past research has

examined the effects of beta-blocker administration on affect, acute stress, and/or mood disorder symptoms, with propranolol being the most widely used. Propranolol is a highly lipophilic, non-selective beta-blocker, meaning that it can cross the blood-brain barrier easily and blocks the binding of epinephrine and norepinephrine across all types of beta-adrenergic receptors. In treatment, it has been mostly used to reduce hypertension, tachycardia, and muscle tremors but is sometimes prescribed off-label to reduce anxiety in acutely stressful situations such as musical performances or public speaking (9). Despite this off-label use, a long history of experimental evidence remains equivocal about the effects of propranolol (and other types of beta-blockers) on subjective ratings of anxiety, stress, and affect (24-51).

Mixed findings may be due to several limitations of prior research. First, most studies are likely underpowered. Specifically, the effect size for propranolol on affect is probably small, yet propranolol groups in most studies are $n<20$ (**Table S1** in **Supplemental Digital Content** or SDC). Furthermore, emotion, affect, or subjective stress are inconsistently measured. Studies tend to focus on a narrow subset of feelings (e.g., state anxiety, single-item stress ratings), suggesting that null effects could be driven by impoverished measurement. Indeed, people tend to report a range of feelings during stressors in addition to anxiety and fear, including anger, embarrassment, and shame (51), yet these other emotions have remained largely ignored in past beta-blockade work. Effects are further complicated by some studies examining drug effects on affect only at rest and other studies examining drug effects only in reaction to a stimulus (e.g., stressor). To address these ambiguities, we assessed the effects of propranolol on a variety of emotional states, ranging in valence and arousal, both at rest (pre/post drug) and with respect to acute stressor reactivity (pre/post stressor). Lastly, although appraisals are another oft-measured dimension of subjective stress (52), to our knowledge, there are no published findings on the effects of propranolol on stress appraisals. Thus, we aimed to provide initial evidence clarifying the effects of beta-blockade on appraisals.

Given that stressors also impact physiology and health, it is critical to examine *both* subjective and physiological changes in parallel. Consequently, we assessed the extent to which beta-blockade impacts autonomic and neuroendocrine markers of the SNS, parasympathetic nervous system (PNS), and

hypothalamic-pituitary-adrenal (HPA)-axis, which are known to shift during acute stressors. This allowed us to disambiguate specific effects of beta-blockade on the reactivity of several physiological systems implicated in stress. As our primary SNS indicator, we measured pre-ejection period (PEP), a cardiovascular measure of sympathetic influence on the cardiac cycle. We also measured salivary alpha amylase (sAA), given that it may in part reflect SNS activity (53,54). Although classic work shows that beta-blockade lengthens PEP at rest, during physical exercise, and under cognitive load (55–58), prior work examining the effects of beta-blockade *under psychosocial stress* (i.e., the Trier Social Stress Test or TSST) has not examined PEP, instead focusing on blood pressure (BP) and heart rate (HR) or neuroendocrine measures such as sAA and cortisol (17,19,20,44-46). We additionally tested the specificity of beta-blockade on SNS vs. PNS reactivity (62) by assessing respiratory sinus arrhythmia (RSA), a marker of parasympathetic cardiac influence. Finally, we built on prior work examining effects of beta-blockade on HPA-axis markers such as cortisol (39,60,63,64), in order to clarify whether past null effects are replicable while further confirming that the effects of beta-blockade are SNS-specific.

To test the above hypotheses and gaps in the literature, we used a preregistered, double-blind, randomized, placebo-controlled design and manipulated beta-adrenergic signaling via administration of a single 40 mg dose of propranolol (n=43) vs. placebo (n=47) prior to the TSST (65). Drawing on diverse tools from psychopharmacology, psychophysiology, and affective science, we used comprehensive, repeated measures of emotions, appraisals, autonomic psychophysiology, and salivary markers in a sample size that more than doubles that of most prior studies. We hypothesized that TSST exposure would result in increased unpleasant, high arousal emotions (e.g., anxiety, anger), and that pre-treatment with propranolol would blunt the intensity of these feelings. To determine specificity, we also examined negative, low arousal emotions (e.g., *boredom*), positive, high arousal emotions (e.g., *excitement*) and positive, low arousal emotions (e.g., *contentment*). We further explored the effects of beta-blockade on TSST appraisals, clarifying whether beta-adrenergic signaling contributes to affect only or if it also influences how people evaluate stressors. Although we hypothesized that beta-blockade should alter affect, it was less clear whether beta-blockade would alter appraisals given the lack of prior research in

this area. One possibility is that appraisals may be less sensitive to in-the-moment neurophysiological fluctuations relative to affect, as appraisals may draw more upon schemas about the situational features of stressors (52,66). Finally, we predicted that propranolol would blunt SNS reactivity but sought to contrast this specificity against PNS and HPA reactivity.

Method

Participants

Ninety healthy young adults (44% female; 56.7% White; M_{age}: 20.29 ± 1.46 years, 18-25 years; M_{BMI}: 22.78 ± 2.47 kg/m², 18.5-28.9 kg/m²; **Table 1**) were recruited from the University of North Carolina at Chapel Hill and its surrounding community via flyers, class announcements, and listservs. Eligibility was assessed via telephone interviews. Individuals were excluded if they reported prior use of beta-blockers, a history of mental or physical health problems, regular nicotine or recreational drug use, prescription medication use, pacemaker or cardiac irregularities, BMI over 33 kg/m², or resting HR/BP below propranolol safety guidelines (< 60bpm, 80mm/Hg). Participants were instructed to come to the lab well-hydrated, having eaten a normal meal, and refraining from caffeine, high sugar, or exercise that day. On the session day, participants had to report good health, no use of over-the-counter medications, and must exhibit a resting HR/BP within the safety cutoff range. Below we describe procedures and measures but see **SDC** for further details and CONSORT diagram.

Procedure

The study was pre-registered with ClinicalTrials.gov (Trial ID: NCT02972554) and approved by the university's institutional review board. After informed written consent, all participants completed the study from 12-5 PM, with procedures time-matched to control for diurnal effects (e.g., cortisol). See **Figure 1** for timeline. Each participant was randomly assigned to receive either a single 40 mg dose of propranolol or placebo, self-administered orally under supervision. We chose a 40 mg dose given that this is both a common dosage used in prior studies with healthy adults (28,37,40) and given that this is a common dosage for one-time performance anxiety situations. Drug randomization was completed and provided in identical capsules by the university's Investigational Drug Services Pharmacy. Staff and

participants were blind to condition, except the study physician (SMB), who remained on call for participant safety but did not interact with participants or researchers. Importantly, all participants remained in their originally assigned conditions, and there were no changes to study design, selection and exclusion criteria, or procedures.

Participants completed the TSST during the 1-2 hours following oral administration of propranolol, when propranolol effects are strongest (67). Participants had 2-min to prepare a speech about their dream job, then gave that speech for 10-min in front of a panel of neutral evaluative judges, whereafter they completed 5-min of impromptu verbal arithmetic (serial subtraction). Participants rated their emotions at baseline before drug administration (pre-drug baseline or BL1), 60-min after drug administration (post-drug baseline or BL2), immediately after TSST speech preparation, and immediately after the full TSST ended. Appraisals were assessed at TSST prep and post-TSST. We measured autonomic changes continuously across six epochs: 5-min BL1, 5-min BL2, 2-min TSST prep, 10-min TSST speech, 5-min TSST arithmetic task, and 7-min recovery post-TSST. Finally, participants provided passive drool saliva samples at BL1, BL2, plus 15-min and 30-min following TSST completion (T15 and T30). Blood samples for inflammatory markers were also collected, but results are published elsewhere (68). See also other work examining separate, secondary questions with this data (69). All participants were debriefed, paid (US$100), and discharged once physiological vitals returned to baseline.

Measures

Self-Reported Emotions. We used an expanded 40-item version of the Positive & Negative Affect Schedule (PANAS; (70)). Participants rated how intensely they were experiencing each emotion on a Likert scale from 1 (*not at all*) to 5 (*extremely*). Following prior standardizations (71,72), mean scores covered the four quadrants of negative, high arousal (e.g., *stressed*), negative, low arousal (e.g., *bored*), positive, high arousal (e.g., *excited*), and positive, low arousal (e.g., *relaxed*). See **SDC** for all items.

Self-Reported Appraisals. We focused on *challenge* and *threat appraisals*, thought to occur when an individual perceives a situation to be challenging but manageable vs. threatening without

sufficient coping resources (73,74). Challenge-threat appraisals were collected immediately after TSST prep and post-TSST, with 6 items for challenge appraisals (e.g., "*I have the abilities to perform the upcoming task successfully"*) and 6 items for threat appraisals (e.g., "*The previous task was very demanding"*) on a Likert scale from 1 (*strongly disagree*) to 7 (*strongly agree*). As a third, more diverse appraisal measure, we assessed participants' negative evaluations of the self and the stressful situation. This negative appraisal measure presented 25 negative descriptors capturing evaluations of personal responsibility for performance (internal attributions or self-evaluations, e.g., blame, incompetence, failure) vs. appraisals about the situation's controllability and unexpectedness (external attributions or evaluations of the experimenters and situation, e.g., unfair, wronged), on a Likert scale from 1 (*not at all*) to 6 (*extremely*). Finally, as a more direct measure of participants' evaluations of the TSST itself, participants rated on 6-items how difficult, stressful, and enjoyable they found the speech and math tasks (e.g., "*The math task was difficult"*) on a Likert scale from 1 (*not at all*) to 6 (*extremely*). As the negative appraisals and TSST task ratings queried how participants perceived how the TSST went, these were only administered post-TSST. See **SDC** for further details.

Autonomic Psychophysiology. To assess sympathetic and parasympathetic activity, we collected continuous electrocardiography (ECG) and impedance cardiography (ICG) at a sampling rate of 1000 Hz using Mindware Technologies (Gahanna, OH, USA). Data for analyses were drawn from the last minute of each baseline, the first minute from each stress phase (preparation, speech, arithmetic), and the last minute of recovery. PEP, a marker of SNS-specific influence on the heart (75), captures the length of time (*ms*) between the onset of depolarization and the start of left ventricular contraction. Shorter (smaller) PEP values suggest faster periods of cardiac contractility via SNS signaling. RSA is characterized as heart rate variability (HRV) synchronized with the respiratory cycle, wherein the R-to-R interval (the length of time between heartbeats) is shorter (faster) during inhalation and longer (slower) during exhalation. Prior studies suggest that RSA reflects parasympathetic influence of the vagus nerve on the heart (76). Higher RSA values suggest less withdrawal of the PNS. In addition to PEP and RSA, we extracted mean HR (beats per minute or bpm) given its prevalence in past research on beta-blockade and stress. However, HR

is a general measure that incorporates both SNS and PNS contributions; as such, we do not focus on HR in the main text (see **SDC**). HR was used as a covariate in models with RSA, given recent recommendations (77). Finally, respiration was estimated from ICG to parse apart respiration from RSA but was not otherwise analyzed. See **SDC** for further discussion of ECG/ICG measurement, scoring, and reliability.

Salivary Measures. Saliva samples were frozen and stored at -80°C until analysis. Salivary concentrations were assessed using commercially available chemiluminescence immunoassay with high sensitivity (IBL International, Hamburg, Germany) following manufacturer instructions. Cortisol was analyzed in duplicate, sAA in singlet. The inter- and intra-assay coefficients of variation for cortisol were both <8%; the inter-assay coefficient of variation for sAA was <6%.

Covariates. Participants self-reported weight and height, from which BMI was calculated and included in all models (78). Additional covariates were sex and socioeconomic status (SES; operationalized as mean years of parental education), given work showing that both alter stress reactivity (79). For salivary models, we adjusted for the menstrual cycle (menstrual, follicular, ovulation, or luteal phases estimated from participants' reported first day of their last period and cycle length), given work showing that stage of menstrual cycle alters HPA reactivity (80).

Statistical Analyses

Cortisol and sAA were log-transformed, given their right-skewed distribution. We also examined and excluded outliers that were ± 3 SDs from the mean on any measure within each timepoint within each condition; there were only a few such outliers with most timepoints across measures having no outliers. All data were analyzed in R using the *lme4* package (81). As timepoints are nested within individuals, we used multilevel modelling with the inclusion of a random intercept to model individual differences in each outcome. For analyses, drug was coded 0=Placebo, 1=Propranolol and, consistent with other psychology studies, sex was coded 0=Female, 1=Male. Additionally, we aggregated across the TSST speech and math tasks for our index of reactivity during the active stressor but examined TSST prep as its own timepoint, as it likely reflects anticipatory stress. We conducted analyses both with respect to the pre-

drug baseline (BL1) and post-drug baseline (BL2) as these test different questions. Analyses with respect to BL1 serve as a manipulation check while also testing the effects of propranolol on our outcomes of interest during a neutral resting state (from pre-drug to post-drug baselines). Analyses with respect to BL2 provide a purer test of how propranolol, once in effect, alters reactivity to the stressor. Throughout the main text, we report most results with respect to BL2, given that this is the strongest test of drug effects on reactivity. In a few cases, we also report manipulation checks comparing BL1 to BL2 but are here careful to specify which baseline is being discussed. See **SDC** for BL1 results.

Results

Multilevel models were used to assess the main effects of *timepoint* (i.e., baseline and task effects), main effects of *drug*, and *timepoint x drug* interactions on emotion and appraisal reports, sympathetic reactivity (i.e., PEP), parasympathetic reactivity (i.e., RSA), sAA reactivity, and HPA-axis reactivity (i.e., cortisol). Conditions were matched on sex, age, and race/ethnicity (**Table 1**) and did not differ on depressive or anxiety symptoms, recent perceived life stress, fear of evaluation (SDC Table 2), BMI, or SES. Unstandardized coefficients are presented throughout the Results, but confidence intervals and standardized betas (β) are presented in tables, with βs serving as effect size estimates.

Effects on Subjective Stress

Affect. As predicted, we found a main effect of *timepoint* on negative, high arousal emotions (**Figure 2, Table 2**), such that these emotions were more intense following both the speech prep (anticipatory stress), b=.38, SE=.07, p<.0001, and immediately after the TSST, b=.75, SE=.07, p<.0001 relative to the post-drug baseline. During speech prep, the interaction between *drug x timepoint* was nonsignificant (b=-.18, SE=.10, p=.068), but immediately after the TSST, those on propranolol reported lower negative, high arousal emotions relative to those on placebo, b=-.22, SE=.10, p=.026. Interestingly, there was no main effect of *drug* on negative, high arousal emotions from the pre-drug to post-drug baseline when participants were at rest. Specifically, there was no difference in negative, high arousal emotions between propranolol vs. placebo at the post-drug baseline (b=-.03, SE=.08, p=.742 in **Table 2)** nor was there a significant interaction of *drug* x *post-drug baseline* relative to the pre-drug baseline

(*b*=.02, *SE*=.09, *p*=.837 in SDC **Table S2)**, suggesting that propranolol administration did not alter negative, high arousal emotions during a neutral, resting state. As a secondary question, we examined whether propranolol impacted other emotions besides negative, high arousal states. There were significant TSST timepoint main effects on other affective quadrants (e.g., decreased positive, low arousal emotions), but *drug* x *TSST* effects were specific to negative, high arousal emotions (**Table 2**).

Appraisals. As would be expected with the TSST, challenge appraisals decreased from speech prep to post-TSST, *b*=-.55, *SE*=.12, *p*<.0001; negative appraisals also increased over time, *b*=.38, *SE*=.07, *p*<.0001 (**Table 3**). There was no significant change in threat appraisals from speech prep to post-TSST (*b*=.04, *SE*=.12, *p*=.754). Interestingly, beta-blockade did not alter appraisals on any measure nor were any *drug x timepoint* interactions significant (all *bs* <-.30-.17, *ps*>.10). In addition to challenge/threat and negative appraisals, an independent *t*-test revealed no differences in how individuals on propranolol (*M*=3.90, *SD*=.87) vs. placebo (*M*=3.91, *SD*=.79) judged the TSST as being difficult, stressful, or unenjoyable, *t*(88)=.07, *p*=.943.

Effects on Physiology

As expected, PEP was shorter (faster) during both the anticipatory stress (prep) and social evaluative (speech, math) TSST phases relative to the post-drug baseline, *bs*=-10.75, -10.69, *SEs*=2.23, 2.21, *ps*<.0001 (**Figure 2, Table 4**). Critically, propranolol altered PEP both at the post-drug baseline, *b*=9.37, *SE*=3.14, *p*=.003, and throughout the TSST speech and math tasks, *b*=9.68, *SE*=3.24, *p*=.003. Individuals on propranolol showed significantly longer PEP both at rest post-drug (BL2) and during the TSST, relative to placebo, indicating less SNS reactivity among those on propranolol. Beta-blockade did not significantly alter PEP during TSST prep nor post-stressor recovery relative to the post-drug baseline (respectively, *bs*= 5.21, 2.16, *ps*>.10). We also examined *drug* and *timepoint* effects on sAA, a salivary measure under both SNS and PNS control. There were no effects of *drug* nor *timepoint* (respectively, *bs*=-.25, .20, *ps*>.10), but there was an interaction of *drug x timepoint, b*=-.50, *SE*=.18, *p*=.006, such that those on propranolol showed blunted sAA reactivity at 15-min post-TSST compared to the post-drug baseline, relative to placebo. Interestingly, there were no effects of *drug* nor interaction of *drug x*

timepoint on RSA (when adjusting for HR; see SDC for unadjusted effects). Similarly, there were no *drug* nor *drug x timepoint* effects on cortisol reactivity, although we replicated the well-established TSST elicitation of increased cortisol. See **Table 4** and **SDC** for more on RSA and cortisol.

Discussion

We demonstrated that pre-treatment with propranolol altered affective experiences but not appraisals during an acute psychosocial stressor. Specifically, individuals on beta-blockade reported lower negative, high arousal emotions while also exhibiting lower SNS reactivity in response to the stressor, relative to those on placebo. Although consistent with some prior work wherein propranolol blunted anxiety (23,28,32,39,43,44,47,49), the present findings contrast with several studies that did not find blunting of subjective stress (26,27,37,38,41,42,45,46,48,82). These inconsistencies in prior work may be due in part to small sample sizes and narrow measures of subjective stress—issues we sought to address herein. Moreover, the present findings reveal both psychological and physiological specificity in the effects of beta-blockade. Beta-blockade blunted negative, high arousal emotions, PEP, and sAA, but not low arousal emotions, positive emotions, appraisals, nor measures of the PNS or HPA-axis (RSA, cortisol). Together, these findings affirm that beta-adrenergic signaling supports SNS-specific physiological responses while also helping transform a potentially stressful situation into the subjective experience we call "stress."

The experimental design and specificity of findings yield intriguing insights about the nature of emotion and stress. First, these findings may provide tentative evidence for the Jamesian and constructionist hypothesis that the peripheral body can contribute to affect (19–22). Although propranolol crosses the blood-brain barrier and acts on both the peripheral and central nervous systems, ongoing work with beta-blockers that have peripheral-predominant effects are informative. For example, *atenolol* is a hydrophilic beta-blocker that cannot easily cross the blood-brain barrier and is selective to β_1-receptors which predominate in the heart (83). Both older and recent studies suggest that atenolol can exert anxiolytic and arousal-blunting effects (47,83,84), indicating that SNS and related signaling via peripheral beta-adrenergic receptors may influence affect. As such, one possibility of the present findings is that

propranolol blunted affect in part via peripheral beta-adrenergic receptors. However, as we did not design this study to adjudicate between peripheral and central pathways, future work is needed to test the degree to which effects on affect are mediated via peripheral vs. central beta-adrenergic receptors.

Another insight from the present findings is that the effects of beta-blockade on affect were *context-dependent*: propranolol did not alter emotions (of any type) from pre- to post-drug resting baselines, and only mattered in the stressful context. Yet propranolol was physiologically active after administration, modulating SNS activity during the same post-drug baseline, as demonstrated by significantly slower PEP in the propranolol group. These results are consistent with "affect-as-information" and constructionist models in affective science (21,85), which hypothesize that physiological changes can influence psychological states particularly when those changes have relevance for the immediate situation. For instance, recent work showed that another physiological state, hunger, intensified affective perceptions and experiences, but only when individuals were in negative but not neutral or positive affective contexts (86). These findings provide converging evidence that allostatic changes across the body and brain, when made meaningful in a relevant situation, can influence the nature and intensity of affective states.

Although we found that beta-blockade altered affect, it did not alter appraisals of the stressor. Longstanding work finds that appraisals and affect are often correlated (87); this was true herein (see SDC). Indeed, individuals who reported greater negative, high arousal emotions in response to the TSST were more likely to appraise the TSST as a negative event (i.e., they made more negative internal and external evaluations: r=.79, p<.001) and to interpret the TSST as less of a positive challenge (r=-.50, p<.001) and more as a threat (r=.59, p<.001). Despite these associations, propranolol only blunted negative, high arousal emotions while appraisals remained intact. All participants reported appraising the TSST similarly as a stressor, but only those on placebo experienced it as emotionally unpleasant and highly arousing. This may suggest that beta-adrenergic signaling either selectively or more robustly impacts the generation of affective states without necessarily altering cognitive evaluations. Thus, although affect and appraisals are both dimensions of subjective stress, they likely reflect different

underlying processes (e.g., affect may draw more upon ongoing physiology and interoception whereas appraisals may draw more upon stable, *a priori* knowledge or schemas about situational features). Alternative possibilities are that beta-adrenergic signaling (whether central or peripheral) may influence other appraisal dimensions than those measured herein, or there may be other neurophysiological pathways (e.g., HPA-axis) not impaired by propranolol that are still influencing appraisals.

As hypothesized, we also found that propranolol blunted the SNS indicator PEP after drug administration and throughout the stressor. These data provide, to our knowledge, the first empirical demonstration that beta-blockade attenuates PEP reactivity specifically during a psychosocial stressor. We replicated a similar pattern of results with sAA. Although the extent to which sAA can be used as an index of SNS activity vs. a more general autonomic index remains debated (53,54), the present finding that propranolol blunted sAA reactivity replicates prior work (59) and aligns with existing interpretations that sAA is (at least in part) under SNS control. Interestingly, effects of propranolol were specific to PEP and sAA reactivity and did not extend to PNS (RSA) or HPA-axis (cortisol) markers. This specificity is consistent with evidence that beta-adrenergic signaling mediates post-synaptic SNS effects, but not PNS cardiac effects (76). Although past literature has found mixed effects of beta-blockade on RSA (88), recent work argues that it is important to account for HR in RSA analyses to parse out confounding SNS effects (77). Consistent with this possibility, as reported in the SDC, we found a *drug* x *timepoint* effect on RSA in unadjusted models, but this effect was nonsignificant after adjusting for HR. Finally, although cortisol significantly increased in response to the TSST, pre-treatment with propranolol did not alter these effects. To date, prior studies have been equivocal about the effects of beta-blockade on HPA reactivity (39,60,63,64). The present findings are in line with interpretations that cortisol, as an end-product of the HPA-axis, may be less sensitive to SNS signaling, at least in the context of acute psychosocial stress in healthy young adults.

This study has several limitations. First, we administered a single 40 mg dose of propranolol to mimic what is typically prescribed for the treatment of performance-related anxiety, but results may not generalize to chronic propranolol use or different dosages. For example, the effects herein might differ at

another dosage amount (e.g., 60 or 80 mg) or frequency (e.g., across several days). Relatedly, prior null effects of beta-blockade on emotion could be due in part to using other dosages, but this remains unclear given that some prior studies with null emotion effects also used a single 40 mg dose (30,37,40,46). However, one consideration is that stronger dosages (e.g., 80 mg) of beta-blockade may exert more overt physiological effects which could lead to unblinding (89), altering the ways in which participants attribute and report their emotions.

Other limitations include the fact that we only assessed effects in healthy young adults, so results should be replicated in other populations (people with mood disorders; older adults). Because we used more comprehensive measures that took longer to complete than a few items, another limitation is that participants may have shifted to a different state between responding to the first and final item in each self-report period. Future studies could reduce this possibility by focusing on negative, high arousal emotions, given our findings. Another unanswered question is the extent to which beta-blockade alters cross-system inter-connections during conditions of acute stress (e.g., correlations between SNS and PNS indicators). Finally, it should be noted that the pharmacological effects of propranolol on emotion cannot be isolated to the peripheral body, brain, or both. Although propranolol is a non-selective beta-blockade, acting upon all types of beta-adrenergic receptors (e.g., β_1, β_2), it appears to have slightly greater affinity for β_2-receptors (90). Given that atenolol is peripherally predominant and selective to β_1-receptors, future extensions could contrast propranolol and atenolol or other beta-blockers (e.g., nadolol) to triangulate central vs. peripheral effects and the role of beta-adrenergic receptor classes in subjective stress and affect.

In sum, the present study leveraged comprehensive methods and measures from psychopharmacology, affective science, and psychophysiology to clarify the murky literature on beta-blockers, emotion, and stress. We found evidence that beta-adrenergic signaling does indeed causally contribute to affective experiences during an acute psychosocial stressor. Although everyone experiences challenging or difficult life events and daily stressors, growing work emphasizes that it is often *subjective*

stress that is more predictive of downstream health and well-being (6–8). As such, understanding how different neurophysiological systems exacerbate or dampen the stress experience may help reveal why some people have more intense emotional responses to negative life events than others. The present findings affirm that the SNS and related adrenergic/noradrenergic systems help instantiate human affective experiences, while also expanding our mechanistic knowledge about the pathways linking stress and health.

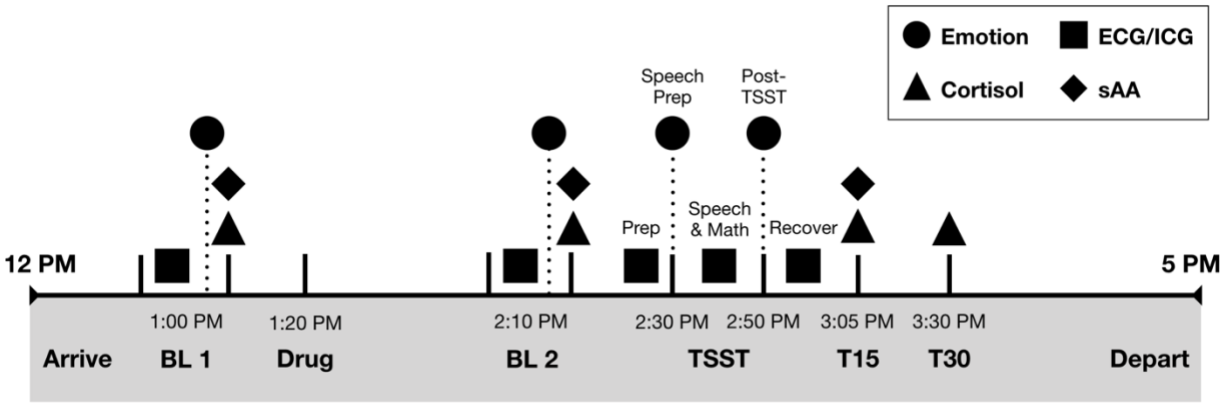

Figure 1. Study timeline illustrating repeated measure timing of self-reported emotions, continuous electrocardiogram (ECG) and impedance cardiography (ICG), and salivary cortisol and alpha-amylase measures. Note that, although not depicted here, appraisals were measured alongside emotion, but only at the TSST Prep and Post-TSST timepoints.

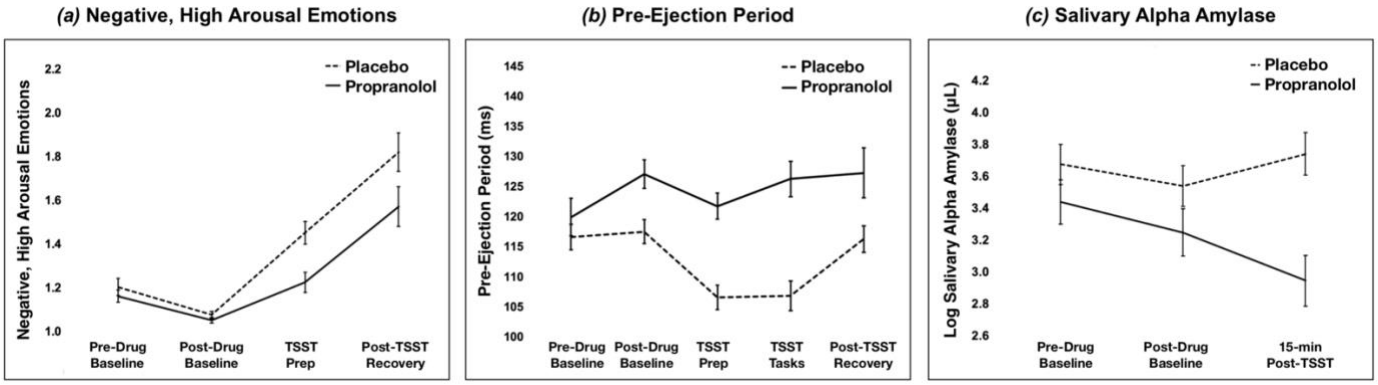

Figure 2. **Placebo vs. propranolol effects across time on (a) negative, high arousal emotions, (b) PEP, and (c) sAA.** Marginal means and standard errors depicted but see Tables 2 and 4 for significant effects. Note that *lower* PEP represents shorter (faster) periods of cardiac contractility, consistent with greater SNS activity.

Table 1. Sample characteristics compared by condition.

Demographics	Placebo	Propranolol	Total	*p*-value
N Sex: Female	21 (23.3%)	19 (21.1%)	40 (44.4%)	.962 [a]
N Sex: Male	26 (28.9%)	24 (26.7%)	50 (55.6%)	
N Race: Asian descent	12 (13.3%)	11 (12.2%)	23 (25.6%)	
N Race: African descent	5 (5.6%)	3 (3.3%)	8 (8.8%)	
N Race: European descent	27 (30.0%)	24 (26.7%)	51 (56.7%)	.876 [a]
N Race: Bi- or multi-racial	2 (2.2%)	4 (4.4%)	6 (6.7%)	
N Race: Other	1 (1.1%)	1 (1.1%)	2 (2.2%)	
Mean Age (years)	20.49 ± 1.56	20.07 ± 1.28	20.29 ± 1.46	.173 [b]
Mean BMI (kg/m²)	23.09 ± 2.43	22.44 ± 2.50	22.78 ± 2.47	.220 [b]
Mean Objective SES	16.52 ± 1.93	16.19 ± 1.89	16.36 ± 1.91	.408 [b]

Note: Frequency counts show percentages of total sample. Objective SES was operationalized as the mean years of education that both parents completed. [a] Difference tested with Pearson's chi-square. [b] Difference tested with independent samples t-tests.

Table 2. Multilevel fixed effects for emotion reports across *drug*, *timepoint*, and *drug x timepoint*.

Predictors	*b*	*β*	*S.E.*	*p*	*Lower 95% CI*	*Upper 95% CI*
Mean negative, high arousal emotions						
Intercept	**1.19**	**.01**	**.283**	**<.001**	**.64**	**1.75**
Drug	-.03	-.17	.084	.742	-.19	.14
TSST Prep	**.38**	**.28**	**.068**	**<.001**	**.24**	**.51**
Post-TSST	**.75**	**.63**	**.068**	**<.001**	**.61**	**.88**
Drug x TSST Prep	-.18	-.09	.099	.068	-.38	.01
Drug x Post-TSST	**-.22**	**-.11**	**.099**	**.026**	**-.42**	**-.03**
Sex	.10	.11	.063	.104	-.02	.23
BMI	-.01	-.00	.023	.975	-.05	.04
SES	-.01	-.04	.017	.530	-.04	.02
Mean negative, low arousal emotions						
Intercept	**.94**	**.01**	**.187**	**<.001**	**.57**	**1.31**
Drug	.08	.13	.053	.129	-.02	.19
TSST Prep	-.06	-.12	.040	.166	-.14	.02
Post-TSST	.01	-.00	.040	.777	-.07	.09
Drug x TSST Prep	-.02	-.02	.058	.718	-.14	.09
Drug x Post-TSST	-.03	-.03	.058	.653	-.14	.09
Sex	.02	.04	.042	.642	-.06	.10
BMI	.01	.04	.015	.666	-.02	.04
SES	.01	.09	.011	.266	-.01	.03
Mean positive, high arousal emotions						
Intercept	**1.81**	**.00**	**.584**	**.003**	**.66**	**2.96**
Drug	.06	.01	.151	.708	-.24	.35
TSST Prep	-.03	-.03	.091	.710	-.21	.15
Post-TSST	.07	.00	.091	.465	-.11	.25
Drug x TSST Prep	-.02	-.01	.132	.891	-.28	.24
Drug x Post-TSST	-.13	-.04	.132	.332	-.39	.13
Sex	**.27**	**.19**	**.131**	**.045**	**.01**	**.53**
BMI	-.02	-.04	.047	.681	-.11	.07
SES	-.01	-.03	.035	.721	-.08	.06
Mean positive, low arousal emotions						
Intercept	**2.48**	**.00**	**.582**	**<.001**	**1.33**	**3.63**
Drug	-.18	-.05	.155	.242	-.49	.12
TSST Prep	**-.56**	**-.27**	**.102**	**<.001**	**-.76**	**-.36**
Post-TSST	**-.61**	**-.35**	**.102**	**<.001**	**-.81**	**-.41**
Drug x TSST Prep	.25	.08	.148	.096	-.04	.54
Drug x Post-TSST	.09	.03	.148	.550	-.20	.38
Sex	.14	.09	.131	.304	-.12	.39
BMI	-.06	-.10	.047	.232	-.15	.04
SES	.01	.03	.034	.740	-.06	.08

Note: Significant effects ($p<.05$) are bolded. SEs are with respect to the unstandardized coefficients.

Table 3. Multilevel fixed effects for appraisals across *drug*, *timepoint*, and *drug x timepoint*.

Predictors	*b*	*β*	*S.E.*	*p*	*Lower 95% CI*	*Upper 95% CI*
Mean challenge appraisals						
Intercept	**3.81**	**.00**	**.791**	**<.001**	**2.25**	**5.37**
Drug	.08	.02	.198	.674	-.31	.48
Post-TSST	**-.55**	**-.31**	**.120**	**<.001**	**-.79**	**-.32**
Drug x Post-TSST	-.10	-.03	.176	.574	-.45	.25
Sex	.17	.09	.179	.351	-.19	.52
BMI	**-.13**	**-.19**	**.064**	**.039**	**-.26**	**-.01**
SES	.05	.11	.047	.254	-.04	.15
Mean threat appraisals						
Intercept	**4.99**	**.00**	**.887**	**<.001**	**3.24**	**6.74**
Drug	-.30	-.12	.217	.172	-.73	.13
Post-TSST	.04	.05	.117	.754	-.20	.27
Drug x Post-TSST	.11	.03	.172	.510	-.23	.45
Sex	-.03	-.01	.201	.895	-.42	.37
BMI	.09	.12	.072	.236	-.06	.23
SES	-.06	-.11	.053	.275	-.16	.05
Mean negative appraisals						
Intercept	**2.14**	**.03**	**.451**	**<.001**	**1.25**	**3.03**
Drug	-.06	-.14	.112	.592	-.28	.16
Post-TSST	**.38**	**.28**	**.070**	**<.001**	**.24**	**.52**
Drug x Post-TSST	-.17	-.08	.102	.102	-.37	.03
Sex	.05	.05	.100	.627	-.15	.25
BMI	-.00	-.01	.036	.935	-.07	.07
SES	-.04	-.15	.027	.116	-.10	.01

Note: Significant effects ($p<.05$) are bolded. Reference category was TSST Prep. SEs are with respect to the unstandardized coefficients.

Table 4. Multilevel fixed effects for physiological measures across *drug, timepoint,* and *drug x timepoint*.

Predictors	*b*	*β*	*S.E.*	*p*	*Lower 95% CI*	*Upper 95% CI*
Mean pre-ejection period						
Intercept	**128.38**	**.00**	**10.714**	**<.001**	**107.30**	**149.46**
Drug	**9.37**	**.42**	**3.143**	**.003**	**3.19**	**15.56**
TSST Prep	**-10.75**	**-.22**	**2.230**	**<.001**	**-15.14**	**-6.36**
TSST Tasks	**-10.69**	**-.16**	**2.214**	**<.001**	**-15.05**	**-6.34**
TSST Recovery	-1.62	-.02	2.247	.471	-6.04	2.80
Drug x Prep	5.21	.07	3.277	.113	-1.23	11.66
Drug x Tasks	**9.68**	**.13**	**3.237**	**.003**	**3.31**	**16.05**
Drug x Recovery	2.16	.03	3.273	.510	-4.28	8.60
Sex	**5.64**	**.17**	**2.477**	**.025**	**.770**	**10.52**
BMI	.67	.06	.905	.465	-1.12	2.45
SES	-.89	-.11	.630	.164	-2.13	.36
Log-transformed salivary alpha-amylase						
Intercept	**1.96**	**-.00**	**.833**	**.021**	**.32**	**3.61**
Drug	-.25	-.25	.203	.220	-.65	.15
Post-TSST T15 (15-min)	.20	-.02	.125	.120	-.05	.44
Drug x T15	**-.50**	**-.13**	**.176**	**.006**	**-.85**	**-.15**
Sex	.06	.03	.230	.788	-.39	.52
Menses Cycle	.03	.04	.077	.713	-.12	.18
BMI	-.08	-.11	.066	.258	-.21	.06
SES	**.10**	**.19**	**.048**	**.049**	**.00**	**.19**
Mean respiratory sinus arrhythmia						
Intercept	**11.39**	.00	**.680**	**<.001**	10.05	12.73
Drug	-.24	-.12	.194	.210	-.63	.14
TSST Prep	.19	.09	.171	.258	-.14	.53
TSST Tasks	.30	.07	.201	.131	-.09	.70
TSST Recovery	-.18	-.04	.160	.275	-.49	.14
Drug x Prep	.06	.01	.231	.792	-.39	.52
Drug x Tasks	-.25	-.05	.242	.305	-.72	.23
Drug x Recovery	.14	.03	.228	.548	-.31	.59
Heart rate	**-.05**	**-.64**	**.005**	**<.001**	**-.06**	**-.04**
Sex	-.26	-.11	.140	.072	-.53	.02
BMI	.01	.02	.050	.797	-.09	.11
SES	-.05	-.10	.036	.142	-.13	.02
Log-transformed salivary cortisol						
Intercept	.66	.00	.647	.311	-.61	1.93
Drug	**.45**	**.21**	**.178**	**.013**	**.10**	**.80**
Post-TSST T15 (15-min)	**.87**	**.43**	**.132**	**<.001**	**.61**	**1.13**
Post-TSST T30 (30-min)	**.60**	**.28**	**.132**	**<.001**	**.34**	**.86**
Drug x T15	-.08	-.02	.190	.693	-.45	.30
Drug x T30	-.10	-.03	.190	.611	-.47	.28
Sex	.33	.18	.178	.070	-.02	.68
Menses Cycle	.00	-.00	.059	.999	-.12	.12
BMI	.06	.10	.051	.216	-.04	.16
SES	-.01	-.01	.037	.893	-.08	.07

Note: Significant effects ($p<.05$) are bolded. SEs are with respect to the unstandardized coefficients.

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Herein, we provide additional details regarding prior literature, methods, results, and discussion that supplement the main text and provide further insights and details. We hope that this additional information will not only increase this study's transparency but also its utility for future research and meta-analyses.

Table S1. Summary of prior literature on propranolol and affect in healthy adults, organized chronologically.

Study	Propranolol Dosage	Sample Size	Context	Affect or Stress Measures	Findings
Turner et al. (1965)	5 mg	Crossover design with: **8** with thyrotoxicosis **8** in an anxiety state	All patients across 4 days given either 5 ml placebo saline, 5 mg propranolol, 5 mg phentolamine, vs. 62.5 mg amylobarbitone sodium	Heart rate during anxiety state (no subjective measure)	Propranolol significantly blunted heart rate during anxiety state compared to placebo or other drugs
Lader & Tyrer (1972)	120 mg	Cross-over design with **6** subjects on 120 mg propranolol, 240 mg sotalol, vs. placebo across three separate days	Various cognitive tests such as reaction time, key tapping, card-sorting, digit symbol substitution test, symbol copying test, etc.	Mood rating scale (16-items) with sedation, contentedness, and anxiety subscales	Propranolol increased drowsiness, "muzziness," and feeling troubled, but not anxiety
Stone et al. (1973)	6 doses of 10 mg	**12** propranolol **12** placebo	Acute stressor of speech task where participants discussed life events that upset, worried or evoked anxiety for them	Post-stressor interview; two independent coders rated verbal samples of the interviews for anxiety	Propranolol reduced anxiety reports post-stressor
Tyrer & Lader (1974)	120 mg	**8** placebo **8** propranolol **8** propranolol (racemic) **8** diazepam	Three stressors including click-shock task, exposure to phobic objects, etc.	Mood rating scale (16-items) with sedation, contentedness, and anxiety subscales	Propranolol reduced anxiety ratings relative to placebo but was less effective than diazepam
Gottschalk et al. (1974)	60 mg	**12** propranolol **12** placebo	Pre- to post-drug at rest; 10-min stress interview	Anxiety ratings	Propranolol reduced anxiety at rest but anxiety during the stressor was equivalent across groups
Ashton et al. (1976)	60 mg	**27** propranolol **27** diazepam **27** placebo	Pre- to post-drug at rest; Acute stressor of mental arithmetic in front of peers	VAS ratings of anxiety	No effect of propranolol on anxiety at rest or post-stressor
Nakano et al. (1978)	40 mg	**24** healthy young men **12** propranolol **12** placebo	Mental stressors: mirror drawing test & Stroop	STAI measures of anxiety pre-drug at rest and post-drug/post-stressor Subjective mood ratings	No effect of propranolol on changes in anxiety or mood post-stressor
Landauer et al. (1979)	80 mg	Cross-over design with **18** healthy young men across 3 days receiving either 100 mg atenolol, 80 mg propranolol, or placebo	Variety of motor and cognitive tests 18 hrs after each dose	"How you feel" measure (22 bipolar adjectives, e.g. sad-happy, lethargic-energetic) POMS mood ratings	When on propranolol, participants rated feeling more gregarious, optimistic, less sorry for themselves, less anxious and less tense compared to when on placebo

Study (Continued)	Propranolol Dosage	Sample Size	Context	Affect or Stress Measures	Findings
Taylor et al. (1981)	80 mg	Cross-over design with **12** healthy young adults on two separate days with propranolol vs. placebo	Experimental stress induced by having participant hold right leg with knee extended above a chair for as long as possible	VAS ratings of anxiety, alertness, and concentration	No effect of propranolol on ratings of anxiety, alertness, and concentration after experimental stress
Brantigan et al. (1982)	Not reported	Cross-over design with **29** music students who on separate days received propranolol vs. placebo	Musical performances in front of other peers and judges	Stage fright self-reports on overall performance, nervousness, & physical symptoms STAI ratings of anxiety	Propranolol reduced state anxiety during the stage performance but did not alter trait anxiety at rest Propranolol reduced nervousness & physical symptoms of stage fright
Hartley et al. (1983)	40 mg	Study 1: Cross-over design with **16** health young adults (8 males, 8 females) high in self-rated trait anxiety; separate lab visits with placebo vs. 40 mg propranolol Study 2 & 3: Cross-over design with **12** healthy young adults high in self-rated state and trait anxiety vs. **12** healthy adults low in state/trait anxiety; separate lab visits with placebo vs. 40 mg propranolol	One minute to prepare for a speech and then 3-min to give a speech in front of a video camera about counterbalanced topics (e.g., anxiety-provoking life experiences; feelings on administering electric shocks to volunteers)	STAI ratings of anxiety Three independent raters also scored the videos for how anxious participants appeared to be from scale 1-20	Study 1: Propranolol reduced both self-reported state anxiety and independently observed anxiety Study 2: Propranolol reduced self-reported state anxiety across both the trait-anxious and non-anxious participants. However, propranolol appeared to reduce independently observed anxiety in the trait-anxious group but not in the non-anxious group
Salem & McDevitt (1984)	40 mg 80 mg 160 mg 320 mg	Cross-over design with **6** young men on 40, 80, 160, and 320 mg of propranolol vs. placebo	Various cognitive tests (e.g., reaction time, digital copying test, symbol digit modalities test, etc.)	VAS ratings of alertness, tension, detachment, and anxiety measured after the cognitive testing ended	At 40 mg, propranolol increased ratings of detachment, and at 80 and 320 mg doses, decreased alertness, but no impact on tension or anxiety
Drew et al. (1985)	120 mg	Cross-over design with **35** medical students who took either propranolol or placebo on two different exam days	Mental arithmetic and verbal reasoning exams	Asked to indicate (post-exam) if they had felt no, mild, moderate, or severe anxiety right before the exam	Propranolol improved exam performance, especially in those who reported that they felt more anxious before the exam

Study (Continued)	Propranolol Dosage	Sample Size	Context	Affect or Stress Measures	Findings
File & Lister (1985)	80 mg	Cross-over design with **17** participants on lorazepam vs. propranolol vs. placebo	Various cognitive tests (e.g., reaction time, digit-symbol substitution, & symbol copying tasks) as well as a 9-min stressor "IQ test"	Mood rating scale (16-items) with sedation, contentedness, and anxiety subscales STAI measure of anxiety post-stressor	No effect of propranolol on mood or post-stress anxiety ratings
Krantz et al. (1987)	.2 mg/kg	Cross-over design with **12** healthy young men on propranolol vs. isoproterenol vs. placebo	Structured interview (speech) and mental arithmetic task	Multiple Affect Adjective Checklist State-Trait Personality Inventory (state-form)	No effect of propranolol (bolus injection) on anxiety, hostility, or anger ratings after a speech and math task
Mazzuero et al. (1987)	120 mg	Male patients with history of myocardial infarction **16** propranolol **16** atenolol **16** chlordesmethyldiazepam **16** placebo	Acute stressor of mental arithmetic plus the Sacks & Levy sentence completion test	STAI measure of anxiety both pre- and post-stressor	No effect of propranolol on anxiety either at rest nor post-stressor
Currie et al. (1988)	40 mg 80 mg 160 mg	Cross-over design with **12** healthy young men taking 40, 80, and 160 mg of propranolol vs. placebo	Cognitive and executive functioning tasks	VAS ratings of wakefulness, tension, calm, energetic, alert, concentration, efficient, irritable, aggressive, sociable, depressed, anxious	Propranolol blunted anxiety
Dyck & Chung (1991)	80 mg	Women undergoing surgery **31** diazepam **32** propranolol **30** placebo	Prior to a surgical operation	STAI ratings of anxiety pre- and post-surgery	No significant differences in anxiety between groups
Jakobsson et al. (1995)	40 mg	Women undergoing surgery **30** ketobemidone **30** lorazepam **30** propranolol **30** placebo	Prior to a surgical operation	Anxiety rated on the Linear Analogue Anxiety Scale	No significant differences in anxiety between groups

Study (Continued)	Propranolol Dosage	Sample Size	Context	Affect or Stress Measures	Findings
Head et al. (1996)	40 mg 80 mg	Cross-over design with **20** young adults, taking placebo, 50 mg metaprolol, 100 mg metaprolol, 40 mg propranolol, & 80 mg propranolol	Treadmill walking exercise	POMS mood and STAI anxiety ratings assessed pre- and post-exercise	Compared to placebo, those on propranolol reported greater tension, depression, and mood disturbances at rest and greater fatigue and confusion both pre- and post-exercise; no drug effect on anxiety
Mealy et al. (1996)	10 mg	Patients undergoing same-day surgery **~25** propranolol **~25** placebo	Same-day surgical procedure	Hospital Anxiety and Depression Scale	Propranolol reduced anxiety on the day of surgery
Elman et al. (1998)	40 mg	**3** young male medical residents performing 40 surgeries on propranolol vs. **33** on placebo (double-blinded)	Surgery performance	Sliding scale rating of how anxious the resident seemed as rated by an attending surgeon observer	For surgeries conducted under propranolol, third-person blinded anxiety ratings were lower than for surgeries conducted under placebo
Harmer et al. (2001)	80 mg	**10** propranolol **10** placebo	Emotion perception task	VAS ratings of tense, angry, sad, happy, alert, & tired Befindlichkeits Scale as additional mood measure	No effect of propranolol on subjective ratings of mood, alertness, or task speed at rest nor when completing an emotion perception task
Rogers et al. (2004)	80 mg	**15** propranolol **17** placebo	Mood ratings taken at rest pre- and post-drug but before a gambling task	PANAS ratings of state negative and positive affect VAS ratings of mental sedation, physical sedation, tranquility, etc.	Propranolol increased feelings of tranquility at rest post-drug, but no effects of propranolol on PANAS ratings at rest
Alexander et al. (2007)	40 mg	Cross-over design with **16** healthy young adults who took propranolol vs. placebo	Acute stressor of the TSST vs. non-stressful control task (reading, counting)	Anticipated stressfulness of the task (pre-TSST but after being informed about it)	No effect of propranolol on anticipated stressfulness of the TSST
Andrews & Pruessner (2013)[a]	80 mg	**15** propranolol **15** placebo	Acute stressor of TSST	Subjective stress rated on a VAS	No effect of propranolol on ratings of stress
Dreifus et al. (2014)	60 mg	**24** propranolol **25** placebo **24** no drug	Pre- to post-drug at rest; Acute stressor as TSST	German versions of the PANAS, SAM ratings of valence and arousal, STAI anxiety ratings, as well as other mood measures	Propranolol blunted state anxiety and arousal ratings at rest. Propranolol reduced TSST-related anxiety, nervousness, and TSST-related changes to well-being and SAM arousal and valence ratings

Study (Continued)	Propranolol Dosage	Sample Size	Context	Affect or Stress Measures	Findings
Ernst et al. (2016)	40 mg	**20** propranolol **20** methylphenidate **20** placebo	Working memory tasks under cognitive load and with conditions of safety vs. threat of shock	STAI anxiety ratings	Propranolol had no effect on changes in anxiety across the tasks
Ali et al. (2017) [b]	80 mg	**22** both dexamethasone and propranolol **22** placebo	Acute stressor of TSST	VAS on "How stressed do you feel right now?" POMS mood ratings	Combined dexamethasone and propranolol group were not significantly different from placebo on stress or mood ratings across time, including post-TSST
Steptoe et al. (2018)	80 mg for 7 days prior	**32** propranolol **32** placebo	Stress tasks of TSST and mirror tracing	HADS (Hospital Anxiety & Depression Scale) to assess anxiety Positive affect subscale of PANAS 7-point single item scale measures of subjective stress and task difficulty	No effect of propranolol on anxiety, positive affect, subjective stress, or task difficulty ratings

Note: We have striven to only include studies here that focused on healthy adults without diagnosed anxiety, phobic, panic, or chronic mood disorders. See Steenen et al. (2016) *Journal of Psychopharmacology* for a review and meta-analysis on the effectiveness of propranolol in treating anxiety and related disorders. [a] **Andrews & Pruessner (2013)** also administered appraisal measures such as the Primary and Secondary Appraisal Questionnaire and the COPE Inventory, but do not report any findings with regards to appraisals (as far as we can find). [b] **Ali et al. (2017)** reported that they likely had sufficient power to detect propranolol effects on subjective ratings by taking the mean of effect sizes for drug effects on physiology (salivary alpha amylase, heart rate, and cortisol) and generating a hypothetical effect size for subjective ratings. This assumes that propranolol impacts psychological phenomenon to the same degree as physiology and that there is close coupling between psychology and physiology. We suggest that the effect size of propranolol on mood is likely much smaller than that of propranolol on physiology, given that drug works directly on physiology but states like emotion or appraisals reflect multiple intra-individual processes besides just physiology. As such, propranolol samples larger than n~20 are likely needed to detect reliable effects on mood/emotion.

Supplemental Information on Study Procedure

Recruitment

Participants were told that the study assessed "physiology and cognition," that propranolol is used to treat hypertension, and that common side effects include feeling lightheaded or dizzy. Participants completed an initial visit to ensure they met health eligibility criteria (i.e., did not have low heart rate or blood pressure) and provided written informed consent. The lab visit occurred three to seven days after this prescreening visit. We were careful to avoid mentioning stress or emotion throughout the study prescreening, intake, and procedures, so as not to bias participants' expectations.

Table S2. Additional sample characteristics compared by condition.

Demographics	Placebo	Propranolol	Total	*p*-value
Mean Depressive symptoms [a]	1.40 ± 1.64	1.30 ± 1.44	1.36 ± 1.54	.755
Mean Anxiety symptoms [b]	37.07 ± 9.20	34.77 ± 7.58	35.96 ± 8.49	.204
Mean Perceived stress [c]	10.62 ± 4.92	10.24 ± 4.60	10.44 ± 4.75	.709
Mean Fear of evaluation [d]	31.28 ± 8.52	33.86 ± 8.86	32.49 ± 8.73	.165

Note: Difference tested with independent samples t-tests. [a] PHQ-9 (Kroenke, Spitzer, & Williams, 2001); [b] State-Trait Anxiety Inventory (Spielberger, Gorssuch, Lushene, Vagg, & Jacobs, 1983), [c] 14-item Perceived Stress Scale (Cohen, Kamarck, & Mermelstein, 1983); [d] brief Fear of Negative Evaluation Scale (Leary, 1983).

Trier Social Stress Test

Participants met two interviewers who were supposedly "experts in the fields of persuasion and nonverbal communication." Participants had 2-min to mentally prepare alone for a 10-min speech about "Why I would be a good candidate for my dream job." After preparation, the interviewers entered the room, sat at a table facing the participant, ostensibly started a video recorder, and the speech began, lasting for 10-min. After the speech ended, the interviewers surprised the participant with an impromptu mental arithmetic task that supposedly assessed their "cognitive capabilities." Participants counted backwards out loud from the number 996 in steps of seven, as quickly as possible. If they made a mistake or lost their place, they were instructed to start again. This task lasted for 5-min. Interviewers wore white laboratory coats and remained neutral and stoic throughout the TSST, providing no feedback but taking copious notes about the performance.

Supplemental Information on Study Measures

Autonomic Psychophysiology

For ECG, three non-invasive spot electrodes were placed on the torso (- on the collarbone, + and ground on the lower ribs). For ICG, two non-invasive spot electrodes were placed on the torso and two on the back. ECG and ICG were collected continuously at a sampling rate of 1000 Hz. Two of the authors (EAC, MMG) visually inspected and independently scored all data, with disagreements resolved by the first author (JKM). Initial agreement between the two scorers was 97.5% for ECG (based on the number of R-spikes identified per segment) and 87.6% for ICG (based on PEP values per segment). RSA was calculated from high frequency HRV after parsing out respiration. Respiration was estimated from ICG; all ECG segments were visually inspected to ensure that respiratory values remained within appropriate respiratory bands.

Emotion Reports

Items within each quadrant of the affective circumplex within each timepoint demonstrated acceptable internal reliability ($M\propto$ = .80).

- **Negative high arousal items (16-items)**: *afraid, angry, annoyed, anxious, ashamed, distressed, embarrassed, frustrated, hostile, irritable, jittery, nervous, panicky, scared, stressed, upset*

- **Negative low arousal items (6-items)**: *bored, disgusted, guilty, sad, unhappy, weary*
- **Positive high arousal items (8-items)**: *amused, determined, enthusiastic, excited, happy, inspired, proud, strong*
- **Positive low arousal items (7-items)**: *calm, content, attentive, interested, pleased, relaxed, quiet*

Additional items measured but that were too neutral in valence and thus not included in the means (3-items): *alert, hyper, sleepy*

Appraisal Reports

The prospective/retrospective measure of challenge and threat appraisals included 6 challenge items (Pre-TSST ∝ =.79; Post-TSST ∝ =.73) and 6 threat items (Pre-TSST ∝ =.75; Post-TSST ∝ =.73). All challenge and threat appraisal items were rated on a Likert scale from 1 (*strongly disagree*) to 7 (*strongly agree)*.

The negative appraisal questionnaire listed 25 negative internal/external appraisal descriptors, listed below (Pre-TSST ∝ =.93; Post-TSST ∝ =.90). This measure was included to capture core evaluations of personal responsibility for performance (internal attributions or self-evaluations) vs. appraisals about the situation's controllability and unexpectedness (external attributions or evaluations of the experimenters and the situational features), rated on a Likert scale from 1 (*not at all*) to 6 (*extremely*). These items were: *Defeated, Challenged, Abandoned, Disgraced, Insulted, Incompetent, Cheated, Loss, Failure, Bad news, Lonely, Made a mistake, Offended, Overwhelmed, Rejected, Threat, Thwarted, Wronged, Uncertain, Uneventful, Unfair, Uninteresting, Unknown, Unresolved, Vulnerable*

Finally, participants rated the nature of the TSST on a "Task Appraisal" measure with 6-items assessing how difficult, stressful, and enjoyable participants found the speech and math tasks, respectively: ∝ =.63. For example, participants rated both the speech and math tasks with wordings such as "The math task was difficult" "The speech task was stressful" or "The math task was enjoyable."

Evaluation of Possible Covariates

At BL1, we assessed trait anxiety via the State-Trait Anxiety Inventory (STAI) (Spielberger, Gorssuch, Lushene, Vagg, & Jacobs, 1983), depressive symptoms via the PHQ-9 (Kroenke, Spitzer, & Williams, 2001), recent perceived stress via the 14-item Perceived Stress Scale (Cohen, Kamarck, & Mermelstein, 1983), and evaluation concerns via the brief Fear of Negative Evaluation Scale (Leary, 1983). These measures were included to confirm no group differences (i.e., no randomization failure) for subclinical mood symptoms, perceived life stress, and fear of evaluation. Given that the groups did not differ on any of these measures (see Table S2 above), they were ultimately not included as covariates

Supplemental Information on Study Results

The Problem of Single-Item Stress Reports

Given that prior beta-blockade studies have used single-item measures of stress and found null effects of propranolol (Alexander, Hillier, Smith, Tivarus, & Beversdorf, 2007; Andrews & Pruessner, 2013), we specifically examined task stressfulness ratings to compliment prior research. This measure was a mean score of two stress items from the "Task Appraisal" measure ("How stressful was the speech task you just completed?" "How stressful was the math task you just completed?"). There were no group differences on this measure between the drug vs. placebo groups $t(88)=.60$, $p=.55$, suggesting that participants found the TSST to be similarly stressful in nature regardless of drug condition. This underlines the importance of assessing emotions or more "internal" psychological states, rather than narrowly focusing on one or two-item

reports of stress, which may instead reflect appraisals and perceptions about the external environment (i.e., the task itself) in line with people's cognitive schemas, rather than their affective states per se.

Parasympathetic Nervous System Reactivity

There were no effects of the TSST on RSA, nor was there an effect of propranolol on RSA at BL2 nor any other timepoint during or after the TSST (all *ps*>.10; see Table 4 in main text).

Beyond RSA, we also examined HR to be consistent with other studies exploring the effects of propranolol on reactivity to acute stress. HR results replicated PEP findings, wherein individuals on propranolol had a lower heart rate relative to placebo throughout the TSST prep, main tasks, and recovery periods. See Figure S2 and Tables S2-S3 for more details.

Hypothalamic-Pituitary-Adrenal (HPA) Axis Reactivity

As would be expected in the context of an acute stressor, salivary cortisol was significantly higher at 15-min and 30-min post-TSST relative to BL2 (*bs*= .87, .60, *SEs*= .13, *ps*<.001). We also observed a significant main effect of *drug* at BL2: cortisol was higher in the propranolol group relative to placebo (*b*=.45, *SE*= .18, *p*=.013). There were no *drug x timepoint* interactions at any later timepoint (*ps*>.25), suggesting that propranolol did not buffer against TSST-related cortisol reactivity (Table 4 in main text). However, it is worth noting that there was a small but significant difference in cortisol between the propranolol and placebo groups at BL1, suggesting randomization failure for this particular measure. As such, cortisol results should be interpreted with caution.

Additional Figures and Tables

See below in this document for additional figures and tables.

Discussion

It is worth observing that the specificity of effects of propranolol on SNS markers but not on RSA or cortisol is in line with degeneracy. *Degeneracy* is a common biological principle whereby a system includes mechanistic redundancies in order to promote survival (Edelman & Gally, 2001). For example, in the context of a stressor, it is likely adaptive for organisms to recruit multiple neurophysiological systems (e.g., HPA-axis) when managing metabolic resources to cope with stressful situations, even when one pathway (e.g., beta-adrenergic signaling) becomes disrupted.

Supplementary References

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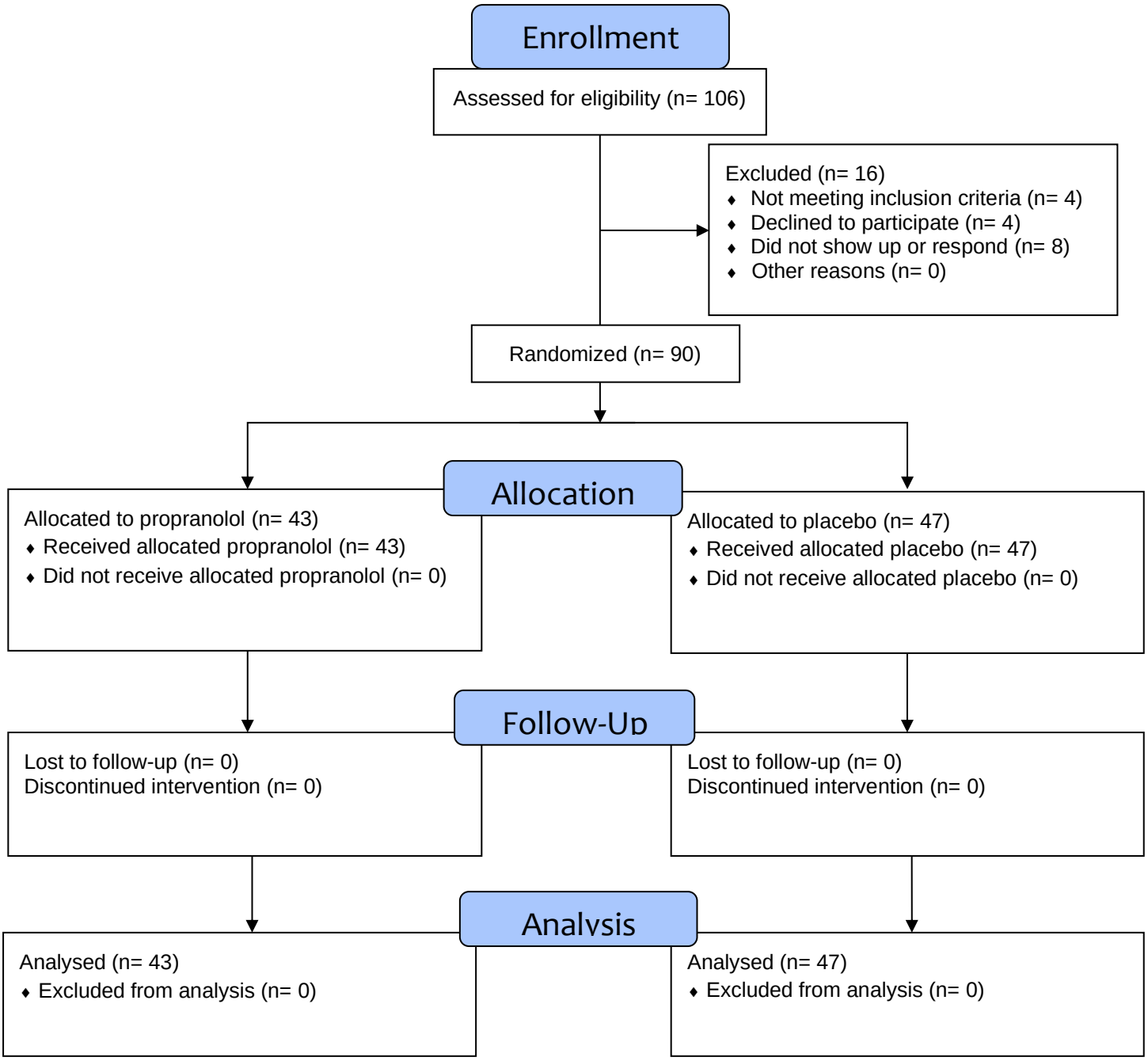
CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



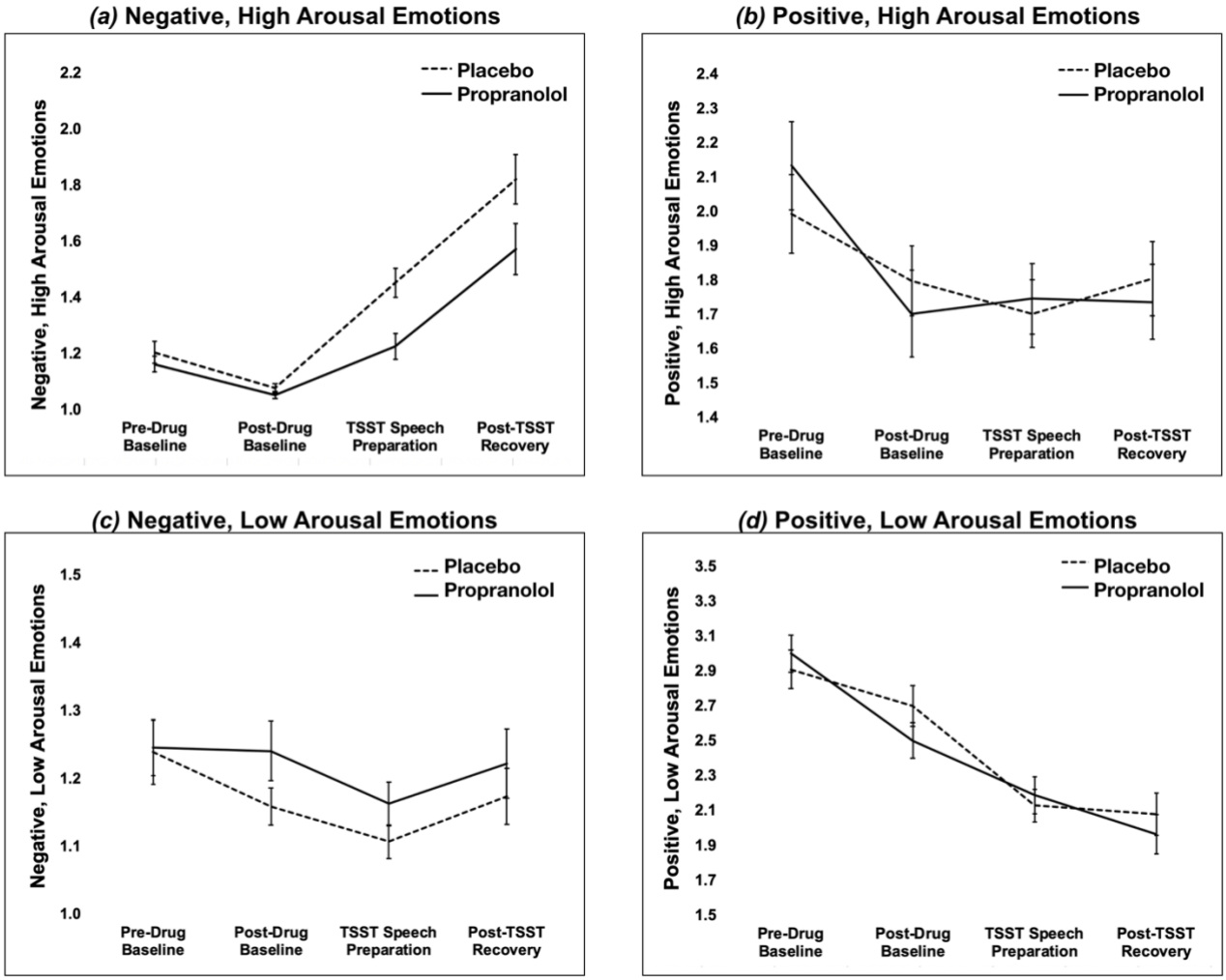


Figure S1. Findings showing effects on (a) negative, high arousal emotions, (b) positive, high arousal emotions, (c) negative, low arousal emotions, and (d) positive, low arousal emotions across measured timepoints with marginal means and standard errors. See Table 2 in the main text for multilevel models assessing statistical significance.

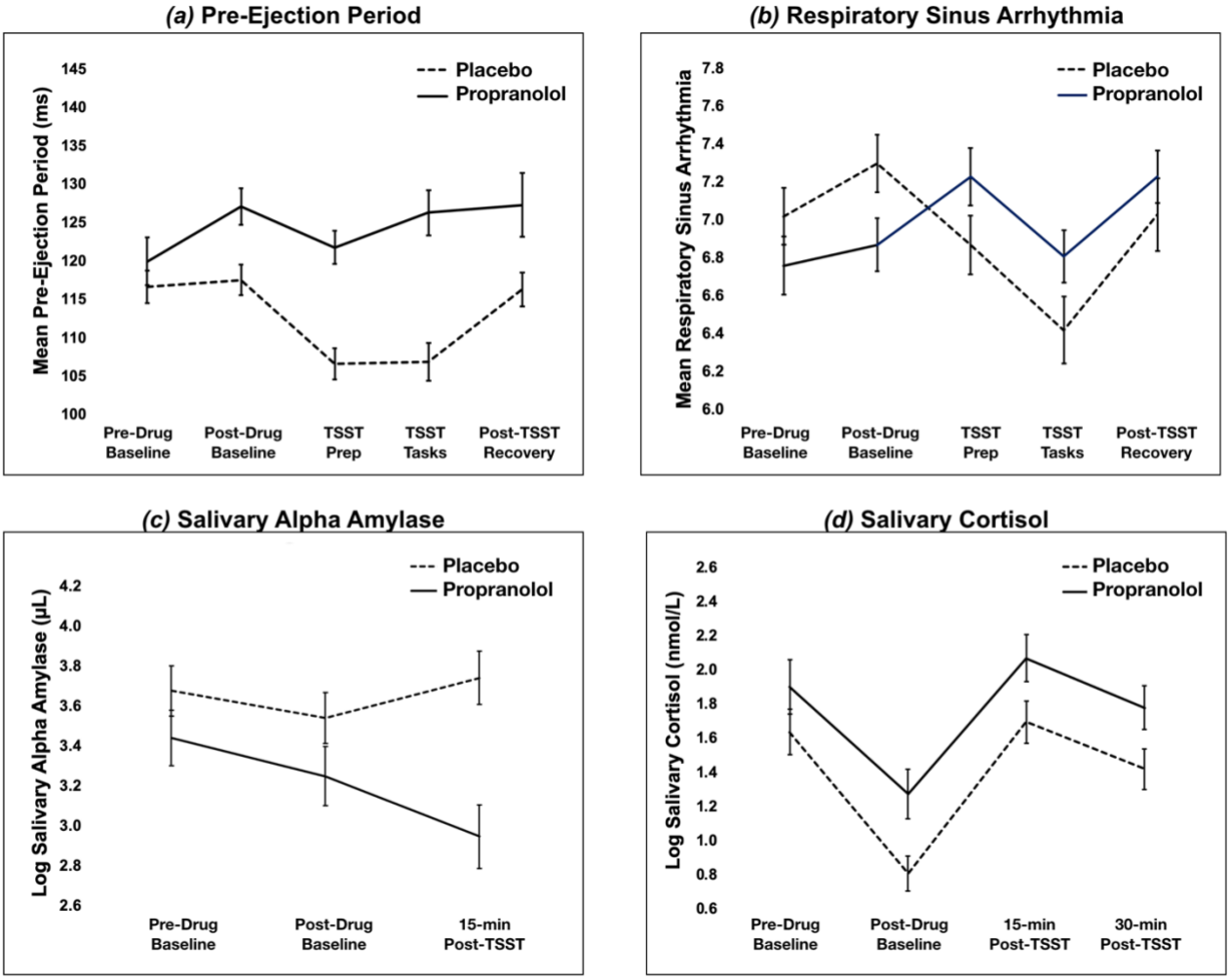


Figure S2. Findings showing effects on (a) pre-ejection period, (b) respiratory sinus arrhythmia, (c) salivary alpha amylase, and (d) salivary cortisol across measured timepoints with marginal means and standard errors. See Table 4 in the main text for multilevel models assessing statistical significance.

Table S3. RSA fixed effects unadjusted for HR, with the post-drug baseline (BL2) as the reference category.

Predictors	*b*	*S.E.*	*p*	*Lower 95% CI*	*Upper 95% CI*
Mean respiratory sinus arrhythmia, unadjusted					
Intercept	**7.31**	**0.16**	**<.001**	**6.99**	**7.63**
Drug (at BL2)	-0.22	0.23	.336	-0.68	0.23
TSST Prep	**-0.44**	**0.19**	**.019**	**-0.80**	**-0.07**
TSST Tasks	**-0.89**	**0.18**	**<.001**	**-1.25**	**-0.53**
TSST Recovery	-0.30	0.19	.106	-0.67	0.06
Drug x Prep	**0.58**	**0.26**	**.028**	**0.06**	**1.10**
Drug x TSST	**0.58**	**0.26**	**.028**	**0.06**	**1.10**
Drug x Recovery	0.45	0.26	.091	-0.07	0.97
Mean respiratory sinus arrhythmia adjusted for all covariates except for heart rate					
Intercept	**8.58**	**0.73**	**<.001**	**7.15**	**10.01**
Drug (at BL2)	-0.24	0.22	.275	-0.68	0.19
TSST Prep	**-0.43**	**0.17**	**.015**	**-0.77**	**-0.08**
TSST Tasks	**-0.88**	**0.17**	**<.001**	**-1.22**	**-0.54**
TSST Recovery	-0.29	0.18	.103	-0.63	0.06
Drug x Prep	**0.57**	**0.25**	**.022**	**0.08**	**1.05**
Drug x TSST	**0.61**	**0.25**	**.015**	**0.12**	**1.09**
Drug x Recovery	0.43	0.25	.083	-0.06	0.92
Sex	-0.01	0.16	.967	-0.33	0.32
BMI	0.00	0.06	.963	-0.11	0.12
SES	-0.08	0.04	.076	-0.16	0.01

Note: Significant effects ($p<.05$) are bolded. Drug was coded 0=Placebo, 1=Propranolol. "TSST Tasks" are the Speech and Math tasks aggregated. Sex was coded 0=Female, 1=Male. Effects here are unadjusted for heart rate. Even after adjusting for the covariates of Sex, BMI, and SES (parental education), there are significant interaction effects of Drug x TSST that disappear when heart rate is added to the model (see Table 4 in main text).

Table S4. Emotion fixed effects, with the pre-drug baseline (BL1) as the reference category.

Predictors	*b*	*S.E.*	*p*	*Lower 95% CI*	*Upper 95% CI*
Mean negative, high arousal emotions					
Intercept	**1.28**	**0.25**	**<.001**	**0.79**	**1.76**
Drug	-0.05	0.08	.562	-0.20	0.11
Post-Drug BL2	**-0.13**	**0.06**	**.040**	**-0.25**	**-0.01**
TSST Prep	**0.25**	**0.06**	**<.001**	**0.13**	**0.37**
Post-TSST	**0.62**	**0.06**	**<.001**	**0.50**	**0.74**
Drug x BL2	0.02	0.09	.837	-0.16	0.19
Drug x TSST Prep	-0.17	0.09	.065	-0.34	0.01
Drug x Post-TSST	**-0.20**	**0.09**	**.024**	**-0.38**	**-0.03**
Sex	0.09	0.06	.109	-0.02	0.20
BMI	-0.00	0.02	.843	-0.04	0.04
SES	-0.01	0.02	.616	-0.04	0.02
Mean negative, low arousal emotions					
Intercept	**0.96**	**0.19**	**<.001**	**0.59**	**1.34**
Drug	0.02	0.06	.732	-0.09	0.13
Post-Drug BL2	-0.07	0.04	.091	-0.15	0.01
TSST Prep	**-0.12**	**0.04**	**.003**	**-0.21**	**-0.04**
Post-TSST	-0.06	0.04	.174	-0.14	0.03
Drug x BL2	0.06	0.06	.313	-0.06	0.18
Drug x TSST Prep	0.04	0.06	.546	-0.08	0.16
Drug x Post-TSST	0.03	0.06	.609	-0.09	0.15
Sex	0.04	0.04	.414	-0.05	0.12
BMI	0.00	0.02	.989	-0.03	0.03
SES	0.02	0.01	.174	-0.01	0.04
Mean positive, high arousal emotions					
Intercept	**1.97**	**0.60**	**.001**	**0.79**	**3.15**
Drug	0.14	0.16	.376	-0.17	0.44
Post-Drug BL2	**-0.25**	**0.09**	**.006**	**-0.42**	**-0.07**
TSST Prep	**-0.29**	**0.09**	**.001**	**-0.47**	**-0.12**
Post-TSST	**-0.19**	**0.09**	**.033**	**-0.36**	**-0.02**
Drug x BL2	-0.09	0.13	.496	-0.34	0.17
Drug x TSST Prep	-0.10	0.13	.449	-0.35	0.16
Drug x Post-TSST	-0.21	0.13	.107	-0.46	0.05
Sex	**0.33**	**0.14**	**.017**	**0.06**	**0.59**
BMI	-0.03	0.05	.562	-0.12	0.07
SES	-0.01	0.04	.827	-0.08	0.06
Mean positive, low arousal emotions					
Intercept	**2.72**	**0.56**	**<.001**	**1.61**	**3.82**
Drug	0.10	0.16	.526	-0.21	0.40
Post-Drug BL2	**-0.22**	**0.10**	**.034**	**-0.42**	**-0.02**
TSST Prep	**-0.78**	**0.10**	**<.001**	**-0.99**	**-0.58**
Post-TSST	**-0.83**	**0.10**	**<.001**	**-1.03**	**-0.63**
Drug x BL2	-0.28	0.15	.063	-0.57	0.02
Drug x TSST Prep	-0.03	0.15	.827	-0.33	0.26
Drug x Post-TSST	-0.19	0.15	.218	-0.48	0.11
Sex	0.09	0.13	.457	-0.15	0.34
BMI	-0.07	0.05	.149	-0.16	0.02
SES	0.01	0.03	.710	-0.05	0.08

Note: Significant effects ($p<.05$) are bolded. Drug was coded 0=Placebo, 1=Propranolol. Sex was coded 0=Female, 1=Male. TSST Prep effects reflect emotion ratings immediately after the 2-min TSST preparatory period before giving the speech. Post-TSST effects reflect emotion ratings given immediately after the TSST completed.

Table S5. Physiology fixed effects, with the pre-drug baseline (BL1) as the reference category.

Predictors	*b*	*S.E.*	*p*	*Lower 95% CI*	*Upper 95% CI*
Mean pre-ejection period					
Intercept	**129.96**	**10.83**	**<.001**	**108.67**	**151.26**
Drug	4.69	3.29	.156	-1.78	11.15
Post-Drug BL2	1.63	2.29	.476	-2.86	6.13
TSST Prep	**-9.09**	**2.30**	**<.001**	**-13.62**	**-4.56**
TSST Tasks	**-9.09**	**2.29**	**<.001**	**-13.59**	**-4.59**
TSST Recovery	-0.11	2.31	.963	-4.66	4.44
Drug x BL2	4.60	3.37	.173	-2.03	11.22
Drug x Prep	**9.59**	**3.40**	**.005**	**2.90**	**16.27**
Drug x TSST	**14.30**	**3.36**	**<.001**	**7.69**	**20.91**
Drug x Recovery	**6.96**	**3.39**	**.041**	**0.29**	**13.63**
Sex	**5.07**	**2.50**	**.046**	**0.15**	**9.99**
BMI	0.33	0.91	.720	-1.47	2.12
SES	-1.04	0.64	.107	-2.29	0.21
Mean respiratory sinus arrhythmia					
Intercept	**11.04**	**0.69**	**<.001**	**9.68**	**12.40**
Drug	-0.22	0.20	.269	-0.61	0.17
Post-Drug BL2	0.17	0.16	.275	-0.14	0.48
TSST Prep	0.31	0.16	.061	-0.01	0.63
TSST Tasks	**0.37**	**0.19**	**.048**	**0.00**	**0.74**
TSST Recovery	-0.02	0.16	.903	-0.33	0.29
Drug x BL2	-0.03	0.22	.878	-0.48	0.41
Drug x Prep	0.08	0.23	.737	-0.38	0.53
Drug x TSST	-0.21	0.24	.397	-0.68	0.27
Drug x Recovery	0.13	0.23	.560	-0.31	0.58
Heart rate	**-0.04**	**0.01**	**<.001**	**-0.05**	**-0.04**
Sex	-0.23	0.14	.103	-0.51	0.05
BMI	0.00	0.05	.930	-0.10	0.10
SES	-0.06	0.04	.130	-0.13	0.02
Log-transformed salivary alpha-amylase					
Intercept	**2.38**	**0.78**	**.003**	**0.85**	**3.91**
Drug	-0.22	0.20	.261	-0.62	0.17
Post-Drug BL2	-0.13	0.13	.290	-0.38	0.11
Post-TSST T15	0.07	0.12	.601	-0.18	0.31
Drug x BL2	-0.03	0.18	.866	-0.38	0.32
Drug x T15	**-0.53**	**0.18**	**.003**	**-0.88**	**-0.18**
Sex	0.12	0.21	.564	-0.30	0.55
Menses Cycle	0.04	0.07	.570	-0.10	0.18
BMI	-0.07	0.06	.280	-0.19	0.05
SES	0.08	0.05	.095	-0.01	0.16
Log-transformed salivary cortisol					
Intercept	**1.28**	**0.65**	**.050**	**0.01**	**2.55**
Drug	0.29	0.19	.129	-0.08	0.65
Post-Drug BL2	**-0.81**	**0.14**	**<.001**	**-1.08**	**-0.54**
Post-TSST T15	0.05	0.14	.710	-0.22	0.33
Post-TSST T30	-0.22	0.14	.120	-0.49	0.06
Drug x BL2	0.16	0.20	.422	-0.24	0.56
Drug x T15	0.10	0.20	.630	-0.30	0.49
Drug x T30	0.08	0.20	.704	-0.32	0.47
Sex	0.30	0.18	.092	-0.05	0.65
Menses Cycle	0.01	0.06	.834	-0.10	0.13
BMI	0.05	0.05	.291	-0.05	0.15
SES	0.01	0.04	.839	-0.07	0.08

Note: Significant effects ($p<.05$) are bolded. Drug was coded 0=Placebo, 1=Propranolol. "TSST Tasks" are the Speech and Math tasks aggregated. Sex was coded 0=Female, 1=Male.

Table S6. Heart rate fixed effects with pre-drug baseline (BL1) vs. post-drug baseline (BL2) as the reference.

Predictors	*b*	*S.E.*	*p*	*Lower 95% CI*	*Upper 95% CI*
Mean heart rate with respect to BL1 or pre-drug baseline					
Intercept	**61.26**	**8.21**	**<.001**	**45.11**	**77.40**
Drug	1.18	2.22	.597	-3.19	5.54
Post-Drug BL2	-2.40	1.39	.084	-5.13	0.32
TSST Prep	**10.18**	**1.39**	**<.001**	**7.45**	**12.90**
TSST Tasks	**21.95**	**1.38**	**<.001**	**19.24**	**24.66**
TSST Recovery	-0.51	1.40	.713	-3.26	2.23
Drug x BL2	-1.44	1.99	.471	-5.36	2.48
Drug x Prep	**-11.71**	**1.99**	**<.001**	**-15.63**	**-7.79**
Drug x TSST	**-18.92**	**1.99**	**<.001**	**-22.82**	**-15.01**
Drug x Recovery	**-7.12**	**2.00**	**<.001**	**-11.05**	**-3.19**
Sex	**-4.81**	**1.85**	**.011**	**-8.44**	**-1.18**
BMI	0.25	0.67	.711	-1.06	1.56
SES	0.47	0.49	.335	-0.48	1.43
Mean heart rate with respect to BL2 or post-drug baseline					
Intercept	**58.64**	**8.90**	**<.001**	**41.13**	**76.14**
Drug	-0.18	2.35	.939	-4.79	4.43
TSST Prep	**12.67**	**1.43**	**<.001**	**9.85**	**15.49**
TSST Tasks	**24.43**	**1.42**	**<.001**	**21.63**	**27.23**
TSST Recovery	2.08	1.44	.151	-0.76	4.92
Drug x Prep	**-10.37**	**2.04**	**<.001**	**-14.39**	**-6.35**
Drug x TSST	**-17.56**	**2.04**	**<.001**	**-21.56**	**-13.56**
Drug x Recovery	**-5.87**	**2.05**	**.005**	**-9.90**	**-1.84**
Sex	**-5.27**	**2.01**	**.010**	**-9.21**	**-1.32**
BMI	0.18	0.72	.807	-1.24	1.60
SES	0.50	0.53	.346	-0.54	1.54

Note: Significant effects ($p<.05$) are bolded. Drug was coded 0=Placebo, 1=Propranolol. "TSST Tasks" are the Speech and Math tasks aggregated. Sex was coded 0=Female, 1=Male.

Table S7. Unadjusted fixed effects for all outcomes, provided for future meta-analyses.

Predictors	*b*	*S.E.*	*p*	*Lower 95% CI*	*Upper 95% CI*
Mean negative, high arousal emotions relative to BL2					
Intercept	**1.08**	**0.06**	**<.001**	**0.96**	**1.19**
Drug	-0.02	0.08	.778	-0.19	0.14
TSST Prep	**0.38**	**0.07**	**<.001**	**0.24**	**0.51**
Post-TSST	**0.75**	**0.07**	**<.001**	**0.61**	**0.88**
Drug x TSST Prep	-0.18	0.10	.067	-0.38	0.01
Drug x Post-TSST	**-0.22**	**0.10**	**.027**	**-0.42**	**-0.03**
Mean negative, low arousal emotions relative to BL2					
Intercept	**1.16**	**0.04**	**<.001**	**1.09**	**1.24**
Drug	0.08	0.05	.144	-0.03	0.18
TSST Prep	-0.06	0.04	.167	-0.14	0.02
Post-TSST	0.01	0.04	.775	-0.07	0.09
Drug x TSST Prep	-0.02	0.06	.731	-0.13	0.09
Drug x Post-TSST	-0.03	0.06	.651	-0.14	0.09
Mean positive, high arousal emotions relative to BL2					
Intercept	**1.74**	**0.11**	**<.001**	**1.53**	**1.94**
Drug	0.06	0.15	.684	-0.24	0.36
TSST Prep	-0.03	0.09	.717	-0.21	0.15
Post-TSST	0.07	0.09	.459	-0.11	0.25
Drug x TSST Prep	-0.02	0.13	.886	-0.28	0.24
Drug x Post-TSST	-0.13	0.13	.328	-0.39	0.13
Mean positive, low arousal emotions relative to BL2					
Intercept	**2.69**	**0.11**	**<.001**	**2.48**	**2.9**
Drug	-0.19	0.16	.225	-0.49	0.12
TSST Prep	**-0.56**	**0.10**	**<.001**	**-0.76**	**-0.36**
Post-TSST	**-0.61**	**0.10**	**<.001**	**-0.81**	**-0.41**
Drug x TSST Prep	0.25	0.15	.096	-0.04	0.54
Drug x Post-TSST	0.09	0.15	.549	-0.20	0.38
Mean challenge appraisals relative to TSST Prep					
Intercept	**4.66**	**0.14**	**<.001**	**4.39**	**4.93**
Drug	0.06	0.20	.773	-0.34	0.45
Post-TSST	**-0.55**	**0.12**	**<.001**	**-0.79**	**-0.32**
Drug x Post-TSST	-0.10	0.18	.574	-0.45	0.25
Mean threat appraisals relative to TSST Prep					
Intercept	**4.10**	**0.15**	**<.001**	**3.81**	**4.39**
Drug	-0.27	0.22	.206	-0.70	0.15
Post-TSST	0.04	0.12	.754	-0.20	0.27
Drug x Post-TSST	0.11	0.17	.510	-0.23	0.45
Mean negative appraisals relative to TSST Prep					
Intercept	**1.46**	**0.08**	**<.001**	**1.31**	**1.62**
Drug	-0.05	0.11	.658	-0.27	0.17
Post-TSST	**0.38**	**0.07**	**<.001**	**0.24**	**0.52**
Drug x Post-TSST	-0.17	0.10	.112	-0.37	0.04
Mean pre-ejection period relative to BL2					
Intercept	**117.55**	**2.40**	**<.001**	**112.84**	**122.26**
Drug	**9.93**	**3.52**	**.005**	**3.01**	**16.85**
TSST Prep	**-10.84**	**2.53**	**<.001**	**-15.82**	**-5.86**
TSST Tasks	**-10.75**	**2.52**	**<.001**	**-15.69**	**-5.80**
TSST Recovery	-1.69	2.55	.509	-6.70	3.33
Drug x Prep	4.84	3.72	.194	-2.47	12.15
Drug x TSST	**9.58**	**3.68**	**<.001**	**2.35**	**16.81**
Drug x Recovery	2.10	3.72	.572	-5.20	9.41
Mean respiratory sinus arrhythmia relative to BL2					
Intercept	**7.31**	**0.16**	**<.001**	**6.99**	**7.63**
Drug	-0.22	0.23	.336	-0.68	0.23
TSST Prep	**-0.44**	**0.19**	**.019**	**-0.80**	**-0.07**

TSST Tasks	**-0.89**	**0.18**	**<.001**	**-1.25**	**-0.53**
TSST Recovery	-0.30	0.19	.106	-0.67	0.06
Drug x Prep	**0.58**	**0.26**	**.028**	**0.06**	**1.10**
Drug x TSST	**0.58**	**0.26**	**.028**	**0.06**	**1.10**
Drug x Recovery	0.45	0.26	.091	-0.07	0.97
Log-transformed salivary alpha-amylase relative to BL2					
Intercept	**44.76**	**5.26**	**<.001**	**34.38**	**55.15**
Drug	-7.48	7.54	.322	-22.37	7.40
Post-TSST T15	7.27	4.93	.143	-2.48	17.01
Drug x T15	**-15.63**	**7.01**	**.027**	**-29.46**	**-1.80**
Log-transformed salivary cortisol relative to BL2					
Intercept	**3.06**	**0.88**	**.001**	**1.32**	**4.80**
Drug	2.16	1.28	.093	-0.36	4.68
Post-TSST T15	**3.92**	**0.10**	**<.001**	**1.96**	**5.89**
Post-TSST T30	1.92	1.00	.057	-0.05	3.90
Drug x T15	1.57	1.44	.277	-1.27	4.40
Drug x T30	0.59	1.44	.684	-2.25	3.43

Note: Please reach out to the first author (JKM) or senior author (KAM) if you need more details or other effect information for meta-analyses.

Table S8. Bivariate correlations between emotions and appraisals within the TSST Prep and TSST Task timepoints.

	During TSST Prep							Immediately after TSST Speech and Math						
	Self-Reported Emotions				Self-Reported Appraisals			Self-Reported Emotions				Self-Reported Appraisals		
	NegHi	**NegLo**	**PosHi**	**PosLo**	**Challenge**	**Threat**	**Negative**	**NegHi**	**NegLo**	**PosHi**	**PosLo**	**Challenge**	**Threat**	**Negative**
Emotions														
NegHi	-	.49***	.02	-.23*	-.39***	.68***	.69***	-	.54***	-.10	-.28**	-.50***	.59***	.79***
NegLo		-	.03	-.09	-.35***	.28**	.50***		-	-.22*	-.26*	-.42***	.15	.47***
PosHi			-	.66*	.32**	- .31**	-.08			-	.70***	.37***	- .27**	-.12
PosLo				-	.40***	- .48***	-.21				-	.50***	- .36***	-.26*
Appraisals														
Challenge					-	- .43***	-.36***					-	- .32***	-.40***
Threat						-	.57***						-	.58***

Note: NegHi= negative, high arousal emotions; NegLo= negative, low arousal emotions; PosHi= positive, high arousal emotions; PosLo= positive, low arousal emotions; Challenge= challenge appraisals; Threat= threat appraisals; Negative= negative internal and external evaluative appraisals.
***p<.001, **p<.01, *p<.05

Table S9. Bivariate correlations between physiological markers in response to the TSST.

	RSA	**sAA**	**Cortisol**
PEP	.26*	-.27*	.02
RSA	-	-.24*	-.11
sAA		-	-.13

Note: These measures reflect the raw timepoint inter-correlations between markers' peak response to the stressor. For autonomic physiology measures of pre-ejection period (PEP) and respiratory sinus arrhythmia (RSA), this was during the TSST speech and math tasks. For salivary markers, this was 15-min post-TSST for salivary alpha amylase (sAA) and 30-min post-TSST for salivary cortisol. Both PEP and RSA decreased under stress (indicative of greater effort or "stress") whereas sAA and cortisol tended to increase. As might be expected, we found a small correlation between PEP and RSA. Similarly, greater sAA peak was associated with greater PEP and RSA decreases in response to the TSST. Cortisol was unrelated to any other markers. *p<.05