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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: 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).

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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 blockade attenuates 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.”

Keywords

Emotion; Appraisals; Stress; Beta-Blockade; Propranolol; Psychophysiology

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, Supplemental Digital Content [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), there is little work examining the effects of beta-blockade on PEP *under psychosocial stress* (i.e., the Trier Social Stress Test or TSST), with most work 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/m^2, 18.5-28.9 kg/m^2; 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/m^2, 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. 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 interconnections 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflicts of Interest and Source of Funding:

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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

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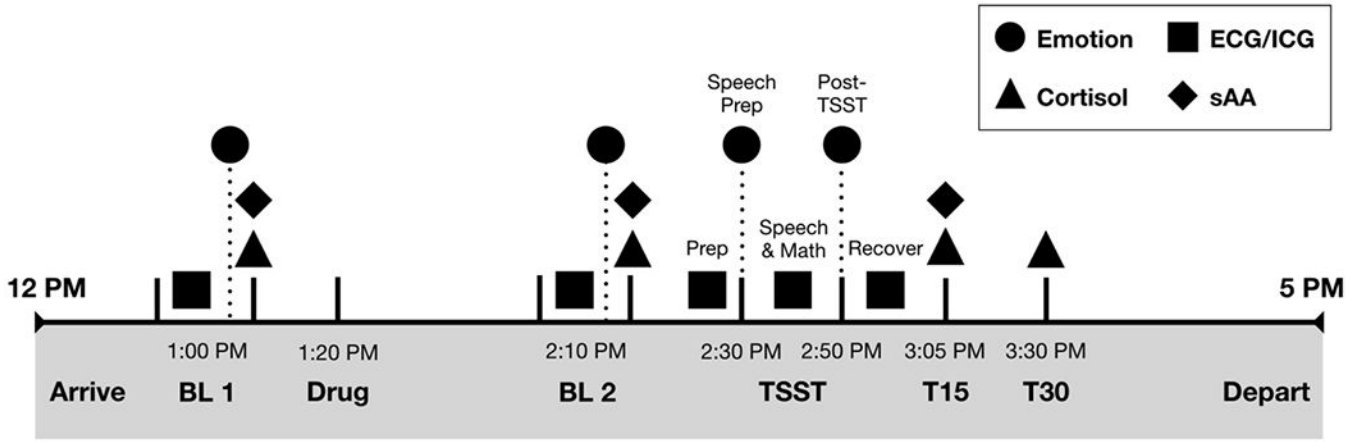

Figure 1.

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.

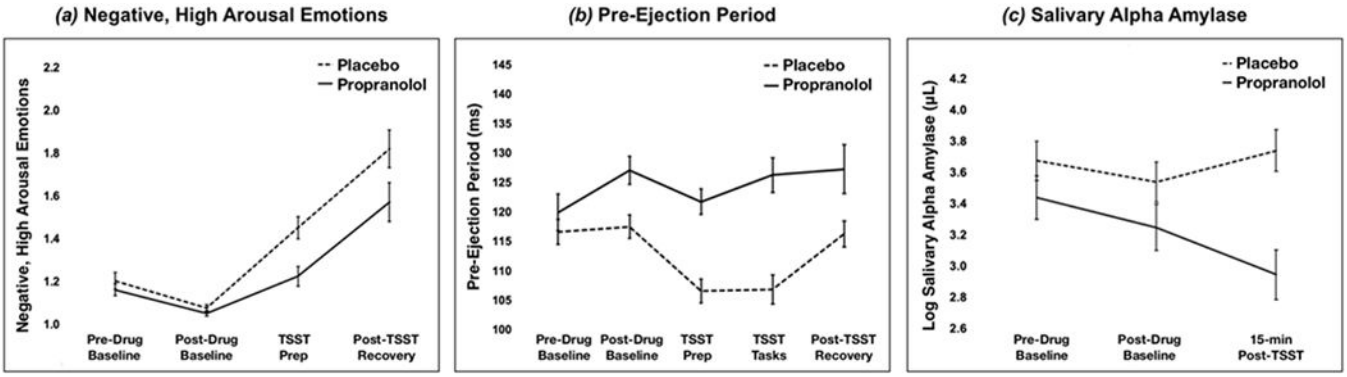

Figure 2. Placebo vs. propranolol effects across time on (a) negative, high arousal emotions, (b) PEP, and (c) sAA.

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
Sex, n (%)				
Female	21 (23.3%)	19 (21.1%)	40 (44.4%)	.962 [a]
Male	26 (28.9%)	24 (26.7%)	50 (55.6%)	
Race n (%)				
Asian descent	12 (13.3%)	11 (12.2%)	23 (25.6%)	.876 [a]
African descent	5 (5.6%)	3 (3.3%)	8 (8.8%)	
European descent	27 (30.0%)	24 (26.7%)	51 (56.7%)	
Bi- or multi-racial	2 (2.2%)	4 (4.4%)	6 (6.7%)	
Other	1 (1.1%)	1 (1.1%)	2 (2.2%)	
Age, mean (years)	20.49 ± 1.56	20.07 ± 1.28	20.29 ± 1.46	.173 [b]
BMI (kg/m^2), mean ± SD	23.09 ± 2.43	22.44 ± 2.50	22.78 ± 2.47	.220 [b]
Objective SES, mean ± SD	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

Predictors	b	β	S.E.	p	Lower 95% CI	Upper 95% CI
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

Predictors	b	β	S.E.	p	Lower 95% CI	Upper 95% CI
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.