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Blood pressure reaction to negative stimuli: Insights from continuous recording and analysis

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Abstract

Individuals with a tendency toward abnormally enhanced cardiovascular responses to stress are at greater risk of developing essential hypertension later in life. Accurate profiling of continuous blood pressure (BP) reactions in healthy populations is crucial for understanding normal and abnormal emotional reaction patterns. To this end, we examined the continuous time course of BP reactions to aversive pictures among healthy participants. In two experiments, we showed participants negative and neutral pictures while simultaneously measuring their continuous BP and heart rate (HR) reactions. In this study, BP reactions were analyzed *continuously*, in contrast to previous studies, in which BP responses were averaged across blocks. To compare time points along a temporal continuum, we applied a multi-level B-spline model, which is innovative in the context of BP analysis. Additionally, HR was similarly analyzed in order to examine its correlation with BP. Both experiments revealed a similar pattern of BP reactivity and association with HR. In line with previous studies, a decline in BP and HR levels was found in response to negative pictures compared to neutral pictures. In addition, in both conditions, we found an unexpected elevation of BP toward the end of the stimuli exposure period. These findings may be explained by the recruitment of attention resources in the presence of negative stimuli, which is alleviated toward the end of the stimulation. This study highlights the importance of continuous measurement and analysis for characterizing the time course of BP reactivity to emotional stimuli.

1 | INTRODUCTION

Exposure to aversive emotional stimuli results in various changes in the autonomic system, such as increased skin conductance (Dimberg, Hansson, & Thunberg, 1998), elevated heart rate (HR) and elevated blood pressure (BP) responses. Despite the evolutionary importance of these autonomic reactions, individuals with a tendency toward abnormally enhanced cardiovascular responses to stress are at greater risk of developing cardiovascular diseases later in life. Therefore, a better understanding of BP response to stressors and aversive stimuli among healthy individuals and among those in disease states is of major theoretical and clinical importance. Nevertheless, the body of literature on BP reactions in the context of aversive settings is rather small compared to the literature discussing other autonomic measures (Dan-Glauser & Gross, 2011; Gianaros et al., 2005, 2008, 2009, 2017; Gianaros, Jennings, Sheu, Derbyshire, & Matthews, 2007; Gianaros, Onyewuenyi, Sheu, Christie, & Critchley, 2012; Gray, Rylander, Harrison, Wallin, & Critchley, 2009; Jennings et al., 2004; McCubbin et al., 2011; Okon-Singer et al., 2014; Pury, McCubbin, Helfer, Galloway, & McMullen, 2004).

Blood Pressure refers to the lateral pressures exerted by blood on the vessel walls. It is expressed in terms of the systolic pressure (maximum pressure during one heartbeat, at the timeframe of around one second) over the diastolic pressure (minimum pressure in between two heartbeats). The role of central regulatory factors, such as baroreceptor function, the influence of midbrain areas on brainstem vascularity, and sympathetic and kidney mechanisms, has been well defined in regulating arterial pressure (Dampney et al., 2003; Grassi & Esler, 2002; Lohmeier et al., 2005; Lohmeier, Dwyer, Irwin, Rossing, & Kieval, 2007). Although BP changes can be measured in a beat-by-beat fashion, existing studies commonly used noncontinuous measurement and analysis strategies that were based on averaging the BP response across stimulation blocks or time-bins or on measuring BP only at the end of the experimental session (Garfinkel et al., 2016; Gianaros et al., 2005, 2007, 2008, 2009; Jennings et al., 2004). Even studies that used continuous BP measurement did not use second-to-second analysis (Gerin, Davidson, Christenfeld, Goyal, & Schwartz, 2006; Gianaros et al., 2012; Gray et al., 2009; Okon-Singer et al., 2014). Although many studies have investigated HR responses using either beat-by-beat or second-to-second measurement and analysis, only a few studies have examined BP responses to psychological stimulation using similar methods.

Therefore, in the current study, we adapted a continuous analysis method and applied it to BP reactions so as to gain a better understanding of the time course of BP reactions to aversive stimuli and to allow for detection of small changes in BP reactivity over time. The importance of specifically examining peripheral BP lies in the possible differences between cardiac (i.e., HR and HR variability) and vascular responses to stimuli. Specifically, such an examination can reveal abnormalities in regulation mechanisms, such as the baroreceptors or peripheral receptors at the level of the brachial artery. Therefore, examination of temporal differences in BP reactions to aversive stimuli is expected to shed light on reaction patterns that cannot be revealed using averaged pre and post stimulation reactions.

For the past several decades, a large body of research has focused on developing continuous and noninvasive BP monitoring systems. Among these methods are the application of an occlusive cuff to measure BP and detect Korotkov sounds or oscillations (Shapiro, Greenstadt, Lane, & Rubinstein, 1981), the volume-clamp method that employs the notion of "vascular unloading" and the pulse transit time method, which describe propagation of the systolic pressure wave through the aorta. To date, the vascular unloading concept has been the most successful and validated technique for continuous noninvasive BP monitoring (Chung, Chen, Alexander, & Cannesson, 2013; Hennig & Patzak, 2013). Therefore, in the current study, we chose to use vascular unloading as the basis for examining a modified continuous analysis method for BP reactivity.

In the current study, we compared BP responses to neutral pictures to responses to negative pictures in an attempt to understand continuous BP reactions to mild negative emotional stimuli. To this end, in two experiments, we showed mixed blocks of negative and neutral pictures to healthy participants. In order to strengthen the reliability of the findings, we employed two different experimental designs using different numbers of blocks and different presentation durations, as well as different resting times. We further measured HR responses in the two tasks in order to examine the correlation between BP and HR responses. *Our goal was to examine an adapted analysis technique that measures BP reactions continuously while comparing different time points along a temporal continuum.* To the best of our knowledge, this study is the first that directly examines the time course of the BP reaction to aversive stimuli.

The few studies that examined the BP reactions to aversive pictures have provided initial evidence of a *decline* in BP levels in response to negative stimuli (Dan-Glauser & Gross, 2011; McCubbin et al., 2011; Okon-Singer et al., 2014; Pury et al., 2004). Based on these studies, we hypothesized that BP levels would decrease in response to negative compared to neutral pictures. We expected that similar patterns would emerge in both studies, providing evidence for the replicability of the findings. Moreover, we expected that the continuous analysis would reveal differences between neutral and negative pictures throughout the time course, which would not be revealed by the classical statistical analysis method.

2 | EXPERIMENT 1

2.1 | Materials and method

2.1.1 | Participants

Running a power analysis for a multilevel model is rather complicated since all the model effects are within-subject and it is impossible to know the exact pattern of the data. Therefore, we ran simulations to estimate the required sample size. The data fluctuations yielded a power of over 80% and type 1 error of 5% with $N = 25$. Twenty-five students (10 females; mean age = 25.76; $SD = 3.66$) from the University of Haifa and the Technion-Israel Institute of Technology participated in the study in return for payment or course credit.

Two BP measurements were taken on separate days within one week to ensure that only individuals with normal BP levels were included (according to Chobanian et al., 2003). On each day, participants' BP at rest was measured three times while they were in a seated position. A mean BP level was calculated for all three measurements. Only participants with mean resting systolic BP levels between 90 and 119 mmHg and diastolic BP levels between 60 and 79 mmHg were included in the study. A third verification BP measurement was taken on the day of the experiment, before the experiment began.

Participants had no history of substance abuse, psychiatric disorders, neurologic diseases, cardiovascular diseases or any other chronic diseases and were not undergoing any pharmacological treatment. Participants were instructed to refrain from physical exercise, smoking and drinking caffeinated beverages 2 hr prior to the beginning of the experiment. The study was approved by the local ethics committee (Approval Number 278/14) and all participants gave their informed consent before the experiment began.

2.1.2 | Stimuli

One hundred sixty pictures from the International Affective Picture System (Lang, Bradley, & Cuthbert, 2008) were chosen based on previous research by Okon-Singer et al. (2014). The pictures were chosen according to valence ratings based on International Affective Norms for participants. Eighty pictures had negative valences (M: 2.35, SD: 0.84) and 80 pictures had neutral valences (M: 5.13, SD: 0.51), based on Okon-Singer et al. (2014). No differences were found between negative and neutral pictures in visual features such as luminance, contrast or dominant spatial frequency. In addition, the content of the pictures (e.g., people, objects) was similar across conditions.

2.1.3 | BP measurement

Peripheral BP (systolic and diastolic arterial BP) was continuously recorded during the task via a double finger cuff as well as an arterial cuff placed on the opposite upper arm. This way, the beat-to-beat measurement from the finger was calibrated using the cuff measurement. This device and procedure have been validated in previous studies (Fortin, Habenbacher, Gruellenberger, Wach, & Skrabal, 1998; Fortin, Habenbacher, et al., 2006; Fortin, Marte, et al., 2006; Jeleazcov et al., 2010) and shown to provide a reliable measure of BP (see also http://www.biopac.com/wp-content/uploads/nibp100d_white_paper.pdf for comparison to intra-arterial BP). BP was measured according to manufacturer recommendations to ensure a reliable signal. The arterial pulse signal was recorded using the NIBP100D-HD device, a bio-physical measurement system (CareTaker unit, Empirical Technologies/ Biopac Systems Inc.; http://www.biopac.com). The signal was transformed in real time to systolic and diastolic BP values using a Pulse Decomposition Analysis algorithm (Baruch, Kwon, Abdel-Rahman, & Isaacs, 2007; Baruch et al., 2011). Data were sampled at a 500 Hz sampling rate.

2.1.4 | HR measurement

HR was continuously recorded during the task using standard 3-lead electrocardiogram (ECG) placement. The signal was sampled at a rate of 1,000 Hz, with a high-pass filter of 0.5 Hz using a Biopac MP150 system (Biopac ECG module, Goleta, CA).

2.1.5 | Procedure

After filling the consent form, participants were prepared for the physiological recordings and BP calibration and were seated approximately 50 centimeters in front of a 23.7 inch computer screen. They were then instructed to look at the screen throughout the experiment and freely watch the pictures that appeared. The experiment began and ended with a 4-min resting period designed to allow participants to relax and become accustomed to the continuous BP measurement and study environment. During that time, participants were asked to sit back and relax while the computer screen displayed the word "rest." After the initial resting period, 16 blocks were presented in randomized order. Each block included a 60-s stimuli exposure period comprising ten trials with neutral pictures or ten trials with negative-valenced pictures (i.e., each block comprised either neutral or negative pictures), followed by 60 s of rest to allow BP to recover. This design was based on an EEG study by Codispoti, Ferrari, and Bradley (2006) in which IAPS pictures were presented while

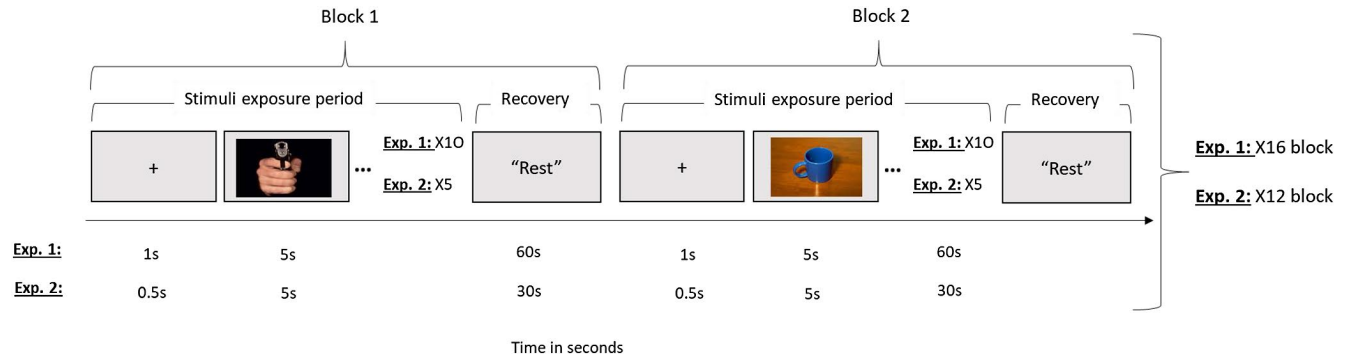

FIGURE 1 Experiment 1+2 design. The procedure for both experiments was similar except for the duration and the number of stimuli presented. The figure shows an example of a block depicting negative-valenced pictures followed by a block depicting neutral pictures. Differences between the two experiments are indicated. Exp. 1:16 blocks containing either neutral or negative-valenced pictures were presented in randomized order (8 blocks of neutral pictures and 8 blocks of negative-valenced pictures). Each block contained a stimuli exposure period that lasted 60s, followed by 60 s of recovery. Each stimuli exposure period contained 10 pictures, either neutral or negative. Each trial during that period began with a fixation cross shown for 1 s, followed by a picture presented for 5 s. Exp. 2:12 blocks containing either neutral or negative pictures were presented in randomized order. Each block contained a stimuli exposure period that lasted 27.5 s, followed by 30 s of recovery. Each stimuli exposure period contained 5 neutral or negative-valenced pictures. Each trial during that period began with a fixation cross shown for 0.5 s, followed by a picture presented for 5 s

the researchers measured HR and skin conductance. Each trial during the stimuli exposure period began with a fixation cross shown for 1 s, followed by presentation of a negative-valenced or neutral picture (depending on the block) at the center of the screen for 5 s (Figure 1).

2.1.6 | Data preprocessing and analysis

BP and HR preprocessing

The preprocessing sequence included the following steps. First, we visually inspected the data for artifact-free blocks. Furthermore, we used a Grubbs' test to detect outliers in each block for each condition. This test is used to detect outliers in univariate data sets assumed to come from a normally distributed population (Grubbs, 1950). BP data cleaning was based on calculating the intervals between the systolic/diastolic peaks and removing peaks inside intervals smaller than 0.3 s or larger than 1.3 s. The HR data were cleaned using the same method, thus eliminating 5% of systolic BP measures, 5% of diastolic BP measures and 4% of HR data from the analysis. Based on evidence indicating that the first presentation of an emotionally charged stimulus causes a different reaction than do other subsequently presented emotional stimuli (Harris & Pashler, 2004), we excluded the first stimulus (i.e., 5 s measured from the onset of the first picture) from each block. Note that even though beat-to-beat changes in response to a single stimulus may be informative, data artifacts may bias the model by increasing the heteroscedasticity affecting the modeled spline structure and covariance matrix, thus potentially resulting in nonconvergence of the model (see "BP and HR responses analysis" section).

A specific baseline for each block was defined as the averaged BP reaction during the 5-s interval preceding the onset of the first picture in each block. Then, for each time point during the block (that includes the 60 s of stimuli exposure as well as the 60 s of the recovery period), BP was calculated as "BP minus baseline" (i.e., the raw BP value at this time point minus the specific baseline of that block). The values of each time point after this baseline correction were included in the B-spline mixed model (see next section below for more details).

BP and HR responses analysis

Classical linear longitudinal models typically involve a single slope growth profile to represent linear changes in an outcome variable across time. Sometimes such a profile does not fit the empirical data. In contrast, B-spline-based mixed-effects models allow flexibility in the modeling of complex patterns across time (Currie & Durban, 2002; Eilers & Marx, 1996). Here, we used a multi-level B-spline model to assess differences in systolic and diastolic BP as well as HR reactions to emotional pictures throughout the time course during stimuli exposure and recovery periods, with B-spline smoothing assessed by the De Boor algorithm (Lee, 1982). The goal of the B-spline model is to find a smooth curve that fits the data. This model exhibits a better fit to the data, but its theoretical justification may be more complex relative to the polynomial alternatives. This statistical approach provides an opportunity to model curvilinear changes in BP and HR as a single process and to test complex effects based on this flexible model. The fit of each model was estimated using Bayesian Information Criteria (*BIC*; Hamaker, van Hattum, Kuiper, & Hoijtink, 2011; Schwarz, 1978) whereby the model with the minimal *BIC* shows the best fit. Models can vary in terms of the optimal number of knots (i.e., complexity of the pattern of fluctuations within a block, defined here as ranging between 0 and 10), the optimal function order (linear, quadratic, or cubic) between knots (Shiyko, Lanza, Tan, Li, &

Shiffman, 2012), several residual distributions of the model outcome (Gaussian, log-normal, Gamma), random intercept and B-spline time course for participants. In addition, we tested the effect of block (i.e., each condition contained 8 blocks and heteroscedasticity of the block effect was tested). The model with the best fit that was chosen for the analysis was based on Gaussian residuals and included four knots with cubic spline, random intercept and random B-spline time effects for participants and blocks as a random effect.

The fixed effects of the model we used included picture valence (i.e., condition) effect, the B-splined time, and the condition X B-splined time interaction. In order to understand this interaction, we further examined the differences in reactions to negative-valenced and neutral pictures at each second using the model-based contrasts (based on Azbel-Jackson, Butler, Ellis, & Van Reekum, 2016) during the 60 s of stimuli exposure as well as during the subsequent 60 s of the recovery period, applying FDR correction for the dependent set of tests (Benjamini & Yekutieli, 2001). Model fit was assessed by a change in *BIC* from a model without the condition X B-splined time interaction. The change in *BIC* is reported in Δ*BIC* and calculated as the *BIC* of the interaction model minus the *BIC* of the model without interaction. According to previous studies, relying only on *p* value for multi-level models is problematic (Hamaker et al., 2011; Wagenmakers, 2007). Therefore, we used Δ*BIC* as a second criterion for model quality. Our decision rule comprised of two criteria: first, the parameter (beta) is significant ($p < .05$); and second, the Δ*BIC* indicated an improvement of the model from a model that is similar only without the interaction term. In addition, model fit was also assessed by the χ^2/df index. The closer the index is to 1, the better the model fit. Finally, the effect size of the model was assessed by calculating marginal R^2 based on Nakagawa and Schielzeth (2013).We also conducted a classical (aggregated) analysis of BP reaction to emotional pictures for purposes of comparison with the B-spline growth curve BP analysis. The mean BP reaction during stimuli exposure was calculated separately for systolic BP and for diastolic BP. A two-sample dependent *t* test analysis compared the reaction between neutral and negative pictures using SPSS (version 23).

Analysis of HR—BP relation

In order to examine a possible relation between BP and HR, we added two analyses. We used the same statistical framework described above and added HR and the interaction between HR and condition to the model in two subsequent steps. In other words, first, we examined the second-to-second covariation between HR and BP. This was done by separately adding HR as a covariate to the multi-level models of systolic BP and of diastolic BP. Second, we examined whether the relation between systolic or diastolic BP is modulated by condition by adding the interaction between HR and condition as another model term to the second model (i.e., the model that includes HR). Note that a simple linear correlation could not be used due to the complex pattern of BP and HR fluctuations over time that must be taken into account. In contrast, our analysis model took into account the effects of task conditions, B-splined time, and their interaction in order to examine the overall covariation between HR and BP across the experiment while eliminating the influence of the other factors. The model does not indicate whether the covariation between HR and BP changes over time. Similar to the other analyses, in addition to testing the significance of the effects, we also checked whether the inclusion of HR and the corresponding interaction of HR and condition resulted in model fit improvement, as assessed by a reduction in Δ*BIC*. If the inclusion of HR or the interaction of HR and condition did not improve the model fit, we would conclude that there was no meaningful relation between BP and HR, even in the presence of a *p* value $< .05$. This was implemented in separate models for systolic BP and for diastolic BP.

The statistical analysis was implemented using the statistical software SAS 9.4 (SAS Institute, Inc., 2012). The model parameter significance criterion was set to 0.05.

Examination of possible interaction with order and gender

Additionally, in order to examine order effects of the stimulation blocks, in the B-spline model, we conducted a three-way interaction between picture valence, B-splined time and block order for systolic and diastolic BP separately. Separate three-way interactions were also conducted between picture valence, B-splined time and gender for systolic and for diastolic BP to examine the possible moderating effect of gender.

2.2 | Results

2.2.1 | Systolic BP reactivity

The multi-level B-spline model revealed a two-way interaction between condition (neutral/negative valence) and time ($F_{(14,336)} = 8.80, p < .0001, \Delta BIC = -116.1$). Further analyses to explain this two-way interaction focused on the differences between the conditions at every second during the stimuli exposure and recovery periods (see Figure 2a and Table S1 in Supporting Information). The systolic BP reaction to negative-valenced pictures differed from the reaction to neutral pictures during large parts of the stimuli exposure and recovery periods (see detailed time points analysis in the Supporting Information). In line with our hypothesis and previous studies (Dan-Glauser & Gross, 2011; McCubbin et al., 2011; Okon-Singer et al., 2014; Pury et al., 2004), a decline in systolic BP was observed in response to negative-valenced compared to neutral stimuli, while the response to neutral pictures did not differ from baseline levels throughout the stimuli exposure period. During the recovery

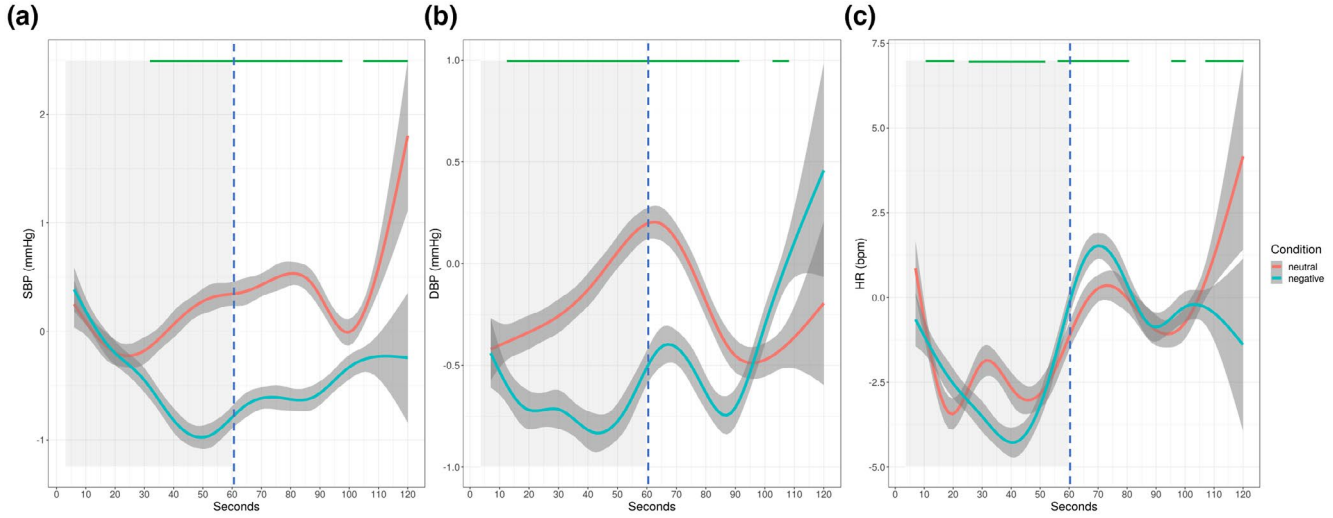

FIGURE 2 Model visualizing BP and HR time course reaction in Experiment 1. A decrease in systolic BP (a), diastolic BP (b) and HR (c) was observed in response to negative-valenced stimuli, followed by recovery. Red represents the reaction to neutral pictures and blue represents the reaction to negative-valenced pictures averaged across blocks during the stimuli exposure (6–60 s; the first 5 s were excluded from analysis, see text for details) and the recovery periods (60–120 s). The green line represents time points with significant differences between conditions. Dotted blue lines mark the end of the stimuli exposure period (after 60 s). The gray areas are 95% confidence intervals. Baseline—defined as the averaged BP or HR during the 5 s before the beginning of each block—was subtracted from the BP or HR values during the stimulation and recovery periods. Note that the first BP/HR response measured during the block is not necessarily equal to the averaged BP/HR in the 5 s before block onset

period, a return to baseline was observed in both conditions, and differences between conditions emerged only toward the end of the recovery period (for a detailed analysis of the time points, see the Supporting Information).

In addition, a visual inspection of the reaction revealed an unexpected enhanced reaction toward the end of the stimuli exposure period. To explore this enhanced reaction, we conducted an additional exploratory post hoc analysis using a contrast based on the initial model. This analysis revealed a significant change between the minimum systolic BP level during the stimuli exposure period and the maximum systolic BP level immediately after the end of the stimuli exposure period ($B = 0.59$, $t(336) = 2.37$, $p < .05$). As can be seen in Figure 2a, a similar pattern displaying an increase in systolic BP levels close to the end of the stimuli exposure period emerged in both conditions. Yet, this reaction was significant only during the neutral ($B = 0.76$, $t(336) = 2.40$, $p < .05$) condition, and not during the negative condition ($B = 0.42$, $t(336) = 1.62$, $p = .10$). The interaction between conditions was *ns* ($B = -0.34$, $t(336) = -1.15$, $p = .25$).

Classical dependent-sample *t* test analysis comparing the averaged systolic BP reaction between neutral ($M = 0.051$, $SD = 0.023$) and negative-valenced pictures ($M = 0.053$, $SD = 0.025$) during the stimuli exposure period did not reveal any significant differences ($t(24) = -0.78$, $p = .44$). This null finding suggests that the changes observed across time in the continuous analysis would have been averaged out in a classical analysis and could not have been revealed by a non-continuous measurement and analysis strategy.

2.2.2 | Examination of possible interaction with order and gender

The multilevel B-spline model did not reveal a three-way interaction between condition (neutral/negative), time and block order ($F_{(16,319)} = 0.58$, $p = .89$), indicating that the pattern of systolic BP responses to time and condition interaction was not affected by the order of the block. In addition, the multilevel B-spline model did not reveal a three-way interaction between condition (neutral/negative), time and gender ($F_{(16,319)} = 1.34$, $p = .16$), suggesting that the participants' gender did not moderate the interaction of interest (time X condition).

2.2.3 | Diastolic BP

The multi-level B-spline model revealed a two-way interaction between condition (neutral/negative) and time ($F_{(14,336)} = 6.45$, $p < .0001$, $\Delta BIC = -74$). As in the analysis of systolic BP, further analyses to explain this two-way interaction focused on the differences between the conditions at every second during the stimuli exposure and recovery periods (see Figure 2b and Table S2 in the Supporting Information). Differences in the diastolic BP reaction between negative and neutral pictures were observed throughout most of the stimuli exposure and recovery periods (see detailed time points analysis in the Supporting Information). As can be seen in Figure 2b, a decrease in diastolic BP levels was observed in response

to negative-valenced stimuli, in line with our hypothesis, while an increase in diastolic BP was observed in response to neutral stimuli. During the recovery period, a return to baseline was observed in both conditions and no differences between conditions emerged until the end of the recovery period, when the systolic BP reaction to negative-valenced pictures was a bit elevated and differences between conditions were observed (for a detailed analysis of the time points, see Supporting Information).

The change between the minimum diastolic BP level during the stimuli exposure period and the maximum diastolic BP level immediately after the stimuli exposure period was also significant ($B = 0.45$, $t(336) = 2.32$, $p < .05$). Although a similar pattern of response was found (i.e., an increase in diastolic BP levels toward the end of the stimuli exposure period), this reaction was only significant in response to neutral pictures ($B = 0.56$, $t(336) = 2.72$, $p < .01$) but not in response to negative-valenced pictures ($B = 0.34$, $t(336) = 1.64$, $p = .10$). The interaction between conditions was *ns* ($B = -0.21$, $t(336) = -1.43$, $p = .15$).

Classical dependent-sample t test analysis comparing the averaged diastolic BP reaction during the stimuli exposure period between neutral ($M = 0.053$, $SD = 0.025$) and negative-valenced pictures ($M = 0.055$, $SD = 0.027$) did not reveal significant differences ($t(24) = -0.70$, $p = .48$). This suggests that, as in the case of systolic BP, changes observed across time in the continuous analysis would have been averaged out in a classical analysis and would not have been revealed via a noncontinuous measurement and analysis strategy.

2.2.4 | Examination of possible interaction with order and gender

Similar to the case of systolic BP, the multilevel B-spline model did not reveal a three-way interaction between condition (neutral/negative), time and block order ($F_{(16,319)} = 0.75$, $p = .74$), again indicating that the pattern of diastolic BP responses to the time and condition interaction was not affected by the order of the block. In addition, the model did not reveal a three-way interaction between condition (neutral/negative), time and gender ($F_{(16,319)} = 1.04$, $p = .43$), indicating that male and female participants reacted similarly in the experiment and the difference in male-female ratio did not affect the patterns of results.

2.2.5 | HR reactivity

The multi-level B-spline model revealed a two-way interaction between condition (neutral/negative) and time ($F_{(14,361)} = 17.38$, $p < .0001$, $\Delta BIC = -285$). Further analyses to explain this two-way interaction focused on the differences between conditions at every second during the stimuli exposure period as well as during the recovery period (see Figure 2c and Table S3 in the Supporting Information). The HR reaction to negative pictures differed from the reaction to neutral pictures during large parts of the stimuli exposure and recovery periods (see detailed time points analysis in the Supporting Information).

2.2.6 | HR and systolic BP relation

The model examining the second-to-second covariation between HR and systolic BP did not reveal any significant relation between them ($B = -0.01$, $F_{(1,37987)} = 3.87$, $p = .05$, $\Delta BIC = 4$). Note that since the inclusion of HR did not improve the model, we conclude that there was no meaningful relation between BP and HR, even though the p value was 0.05 (see Method section for more details). In addition, inclusion of the interaction between HR and condition (negative/neutral) was *ns* ($B = -0.01$, $F_{(1,15314)} = 1.13$, $p = .28$, $\Delta BIC = 6.38$).

2.2.7 | HR and diastolic BP relation

The model examining the ##second-to-second covariation between HR and diastolic BP revealed a positive relation between them ($B = 0.11$, $F_{(1,37854)} = 38.66$, $p < .0001$, $\Delta BIC = -23$). In addition, inclusion of the interaction between HR and condition (negative/neutral) was *ns* ($B = -0.02$, $F_{(1,37839)} = 0.47$, $p = .49$, $\Delta BIC = 4.3$), indicating that the relation found between diastolic BP and HR was not modulated by condition.

3 | EXPERIMENT 2

Due to the innovative nature of the measurement and analysis employed in Experiment 1, we aimed to replicate the findings in Experiment 2. We expected to find a similar pattern of BP response to the picture blocks: a decrease in BP during negative-valenced stimulation and an increase in BP toward the end of the stimulation for both negative-valenced and neutral stimuli. Furthermore, in order to make this task easier to use in a wide range of populations and experimental protocols, we modified it by creating a shorter version. Experiment 1 lasted around 40 min, which may be too long for pre-post treatment protocols as well as for clinical populations.

3.1 | Materials and method

3.1.1 | Participants

Twenty-six students (6 females; mean age = 26.69; *SD* = 4.16) from the University of Haifa and the Technion-Israel Institute of Technology participated in the study in return for payment or course credit. None of the participants in Experiment 2 took part in Experiment 1. All other participant characteristics and BP screening met the same criteria as in Experiment 1.

3.1.2 | Stimuli

Thirty negative-valenced and 30 neutral pictures from the International Affective Picture System (Lang et al., 2008) were chosen in a similar fashion as in Experiment 1.

3.1.3 | Procedure

The experiment began with a 1-min rest period during which participants were asked to sit back and relax while the computer screen displayed the word "rest." After the initial rest, 12 blocks were presented in randomized order. Each block included 27.5 s of stimuli exposure period, during which five neutral or negative picture trials (between blocks) were presented, followed by 30 s of rest to allow BP recovery back to baseline. Each trial in the stimuli exposure period began with a fixation cross shown for 500 milliseconds, followed by presentation of a negative-valenced or a neutral picture (depending on the block) at the center of the screen for 5 s (Figure 1).

3.1.4 | Data preprocessing and analysis

Preprocessing and analysis were similar to Experiment 1. BP and HR data cleaning eliminated 6% of systolic BP readings, 6% of diastolic BP readings and 3% of HR data from the analysis.

In addition, in Experiment 1, BP began elevating toward the end of the stimuli exposure period, reaching a maximum elevation that is higher than baseline immediately after the end of the stimuli exposure period. In Experiment 2, we therefore examined a priori whether a similar pattern emerges. To this end, we compared the differences between minimum BP level during the stimuli exposure period and maximum BP level after the end of the stimuli exposure period.

3.2 | Results

3.2.1 | Systolic BP reactivity

The multi-level B-spline model revealed a two-way interaction between condition (neutral/negative) and time ($F_{(16,400)} = 3.33$, $p < .0001$, $\Delta BIC = -92.2$). Further analyses to explain this two-way interaction focused on the differences between conditions at every second during the stimuli exposure and the recovery periods (see Figure 3a and Table S4 in Supporting Information).

The systolic BP reaction to negative-valenced and neutral pictures differed between groups during most of the stimuli exposure and recovery periods (see detailed time points analysis in the Supporting Information). As can be seen in Figure 3a, a decline in systolic BP levels was

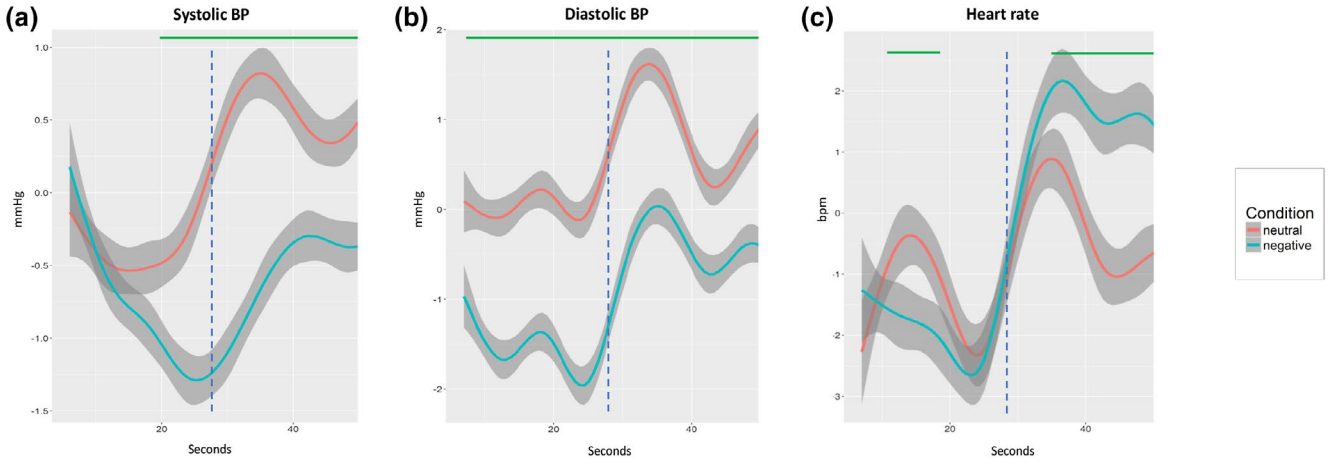

FIGURE 3 Model visualizing BP time course reaction in Experiment 2. A decrease in systolic BP (a), diastolic BP (b) and HR (c) was observed in response to negative-valenced stimuli, followed by recovery. Red represents the reaction to neutral pictures and blue represents the reaction to negative-valenced pictures during the stimuli exposure (6–27.5 s; the first 5 s were excluded from analysis, see text for details) and recovery periods. The green line represents time points with significant differences between conditions. Dotted blue lines mark the end of the stimuli exposure period (after 27.5 s). The gray areas are 95% confidence intervals. Baseline—defined as the averaged BP or HR during the 5 s before the beginning of each block—was subtracted from the BP or HR values during the stimulation and recovery periods. Note that the first BP or HR response measured during the block is not necessarily equal to the averaged BP or HR in the 5 s before block onset

observed in response to negative compared to neutral stimuli, while the response to neutral pictures did not differ from baseline levels throughout the stimuli exposure period. Toward the end of the stimuli exposure period, systolic BP in both conditions was elevated, followed by a return to baseline during the recovery period. While this response pattern seems similar in both conditions, as mentioned above, differences in systolic BP reaction emerged between conditions, indicating a robust response to negative compared to neutral pictures.

Examination of the change between the minimum systolic BP level during the stimuli exposure period to the maximum systolic BP level immediately after the stimuli exposure period was also significant ($B = 1.2$, $t(400) = 4.34$, $p < .0001$). A sharp increase in systolic BP levels toward the end of the stimuli exposure period emerged in both the neutral ($B = 1.34$, $t(400) = 3.77$, $p < .0005$) and the negative ($B = 1.05$, $t(400) = 2.90$, $p < .005$) conditions. The interaction between conditions was *ns* ($B = -0.29$, $t(400) = -0.64$, $p = .52$).

Classical dependent-sample t test analysis comparing the averaged systolic BP reaction during the stimuli exposure period between neutral ($M = 0.055$, $SD = 0.041$) and negative-valenced pictures ($M = 0.058$, $SD = 0.048$) did not reveal significant differences ($t(25) = -0.68$, $p = .45$). This null finding suggests that the changes observed across time in the continuous analysis would have been averaged out in a classical analysis and would not have been revealed via a noncontinuous measurement and analysis strategy.

3.2.2 | Diastolic BP

The multi-level B-spline model revealed a two-way interaction between condition (neutral/negative) and time ($F_{(16,400)} = 5.88$, $p < .0001$, $\Delta BIC = -28.66$). As in the analysis of systolic BP, further analyses to explain this two-way interaction focused on the differences between conditions at every second during the stimuli exposure and recovery periods (see Figure 3b and Table S5 in Supporting Information).

Differences in the diastolic BP reaction between negative and neutral pictures were observed during the stimuli exposure and recovery periods (see detailed time points analysis in the Supporting Information). As can be seen in Figure 3b, these differences reflect an initial decrease in diastolic BP in response to negative-valenced stimuli, while the BP response in response to neutral stimuli did not differ from baseline during the stimuli exposure period. In addition, toward the end of the stimuli exposure period, a similar response was observed for both conditions: a steep increase in diastolic BP levels followed by a decrease in diastolic BP back to baseline levels during the recovery period.

An additional analysis examining the minimum diastolic BP level during the stimuli exposure period to the maximum diastolic BP level immediately after the stimuli exposure period ended was significant, regardless of condition ($B = 1.63$, $t(400) = 5.88$, $p < .0001$). A sharp increase in diastolic BP levels at the end of the stimuli exposure period emerged in both the neutral ($B = 1.73$, $t(400) = 5.47$, $p < .0001$) and the negative ($B = 1.53$, $t(400) = 5.05$, $p < .001$) conditions. The interaction between conditions was *ns* ($B = -0.19$, $t(400) = -0.71$, $p = .48$).

Classical dependent-sample t test analysis comparing the averaged diastolic BP reaction during the stimuli exposure period between neutral ($M = 0.064$, $SD = 0.043$) and negative-valenced ($M = 0.065$, $SD = 0.050$) pictures did not reveal significant differences ($t(25) = -0.02$, $p = .98$). Similar to the case of systolic BP, this suggests that changes observed across time in the continuous analysis would have been averaged out in a classical analysis and would not have been revealed via noncontinuous measurement and analysis strategy.

3.2.3 | HR reactivity

The multi-level B-spline model revealed a two-way interaction between condition (neutral/negative) and time ($F_{(16,400)} = 5.61$, $p < .0001$, $\Delta BIC = -73.2$). Further analyses to explain this two-way interaction focused on the differences between conditions at every second during the stimuli exposure and recovery periods (see Figure 3c and Table S6 in Supporting Information). The HR reaction to negative pictures differed from the reaction to neutral pictures during large parts of the stimuli exposure and recovery periods, indicating differences between conditions in HR reaction (see detailed time points analysis in the Supporting Information).

3.2.4 | HR and systolic BP correlation

The model examining the second-to-second covariation between HR and systolic BP did not reveal a significant relation between them ($B = -0.04$, $F_{(1,15315)} = 4.75$, $p < .05$, $\Delta BIC = 1.44$). Note that since the inclusion of HR did not improve the model, we conclude that there was no meaningful relation between BP and HR, even with a p value $< .05$. In addition, the interaction between HR and condition (negative/neutral), was *ns* ($B = -0.01$, $F_{(1,15314)} = 1.13$, $p = .28$, $\Delta BIC = 6.38$).

3.2.5 | HR and diastolic BP correlation

The model examining the second-to-second covariation between HR and diastolic BP revealed a positive relation

between them ($B = 0.20$, $F_{(1,15197)} = 73.21$, $p < .0001$, $\Delta BIC = -30.79$). In addition, the interaction between HR and condition (negative/neutral), was significant ($B = 0.02$, $F(1,15196) = 10.60$, $p < .005$, $\Delta BIC = -2.13$), indicating that the condition affected the interaction between HR and diastolic BP. Although a similar positive relation was found for both neutral and negative-valenced pictures, the correlation between HR and diastolic BP was slightly stronger for neutral pictures ($B = 0.21$, $t(15196) = 9.05$, $p < .001$) than for negative ones ($B = 0.19$, $t(15196) = 8.27$, $p < .001$).

4 | DISCUSSION

The present study compared continuous BP responses to neutral and negative-valenced pictures in two experiments that differed in their temporal properties. In both experiments, we found a similar pattern of BP reactivity as well as a similar pattern of correlation of systolic and diastolic BP with HR. The replication in Experiment 2, even when the task was shortened and small modifications were made, points to the reliability of the innovative data acquisition and analysis strategies employed in this study. The results revealed a steep decline in systolic and diastolic BP levels in response to negative-valenced compared to neutral pictures. Toward the end of the stimuli exposure periods, for most measures, we found that BP already began to rise and return to baseline levels. The similar pattern across conditions and experiments (i.e., the fact that this elevation begins around two-thirds into the stimuli exposure period, although the length of the stimuli exposure differed between experiments) strengthens the reliability of these findings. As detailed below, these findings may be explained by attentional and expectancy mechanisms.

In contrast to previous studies that averaged BP across trials or blocks (Garfinkel et al., 2016; Gianaros et al., 2005, 2007, 2008, 2009; Jennings et al., 2004), we employed a continuous analysis method. This technique allowed us to reveal differences in BP reaction that were not detected via classical analysis, probably since the revealed pattern of BP (increase and decrease in BP) was averaged across the blocks. Since the time course of the BP reaction to negative-valenced stimuli is still unclear, the use of a nonlinear model that allows for dynamic observation of the BP response as well as examination of time points throughout the experiment are important for revealing subtle differences between populations (Azbel-Jackson et al., 2016).

Currently there are no norms for continuous BP analysis. Therefore, in the absence of any official guidelines, analysis decisions in this study were based on the rather small number of existing studies. Unified measurement and analysis methods have the potential to generate a common basis for further studies and thus make a major contribution to research on peripheral BP reactions. The continuous measurement and analysis employed in this study allowed us to characterize the time course of BP reactivity at a high beat-to-beat temporal resolution. Such resolution facilitated understanding of BP changes as a function of the experimental protocol. Moreover, such an approach has the potential to facilitate a better understanding of the dynamics between the reaction to stimuli and the subsequent recovery. For instance, as opposed to previous studies in which BP reached a maximum level following picture presentation, our data showed the amount of time it took for BP to react as well as to return to baseline level, indicated whether block length influenced BP reactivity.

In the long term, future studies can further examine other populations with abnormalities related to BP, such as individuals with essential hypertension or those at risk of developing cardiovascular dysfunction. Based on studies indicating that the tendency to exhibit abnormally enhanced cardiovascular responses to stress and aversive situations predicts later development of essential hypertension (Deter, Blecher, & Weber, 2007; Deter, Micus, Wagner, Sharma, & Buchholz, 2006; Gianaros et al., 2007, 2012; Gianaros & Sheu, 2009; Jennings et al., 2004; Matthews et al., 2004; Treiber et al., 2003; Ugajin et al., 2005; Yan et al., 2003), it is plausible to hypothesize the emergence of enhanced BP reactions to aversive stimuli among patients as well as among individuals at high risk of developing hypertension. Comparing different tasks in the same population and comparing patients with hypertension to individuals at high risk as well as to healthy controls may shed light on the specific processes that underlie hypertension. Examining these processes is in line with calls for a paradigm ranging from treatment of manifest EH to prevention based on a risk-factor approach (Chobanian et al., 2003; Sacco, Wolf, & Gorelick, 1999). In addition, a better understanding of the time course of BP reaction is critical for planning future studies and can assist in making specific decisions regarding the experimental protocol. This information can facilitate the development of a normative model of BP reactivity in response to emotional stimulation. Such a model can, in turn, make a major contribution to the study of peripheral BP responses by facilitating the creation of experimental protocols. Specifically, understanding how BP reacts to emotional stimuli can assist in increasing the signal-to-noise ratio, thus improving statistical analysis and facilitating short event-related tasks.

Our results replicate previous studies with healthy participants and patients with essential hypertension, who also exhibited a decline in BP levels in response to negative-valenced pictures (Dan-Glauser & Gross, 2011; McCubbin et al., 2011; Okon-Singer et al., 2014; Pury et al., 2004). Similarly, a decline in HR following exposure to negative-valenced pictures has also been demonstrated (Lang, Greenwald, Bradley, & Hamm, 1993; Tooley, Carmel, Chapman, & Grimshaw, 2017; Wangelin, Löw, McTeague, Bradley, & Lang, 2011). These findings suggest that rather moderate negative stimuli lead to

increases in attention and in alertness without the need for a physical motor response, resulting in decreased sympathetic or increased parasympathetic autonomic reaction, including decreased HR and BP levels (Lang, Davis, & Öhman, 2000). Indeed, based on examination of HR and skin conductance reactions in various tasks, Lacey and Lacey (1974, 1978) suggested that sensory intake results in HR deceleration. Similarly, tasks entailing passive viewing commonly yield a decrease in cardiovascular responses (Bohus et al., 1987; Lehrer et al., 1996; Schneiderman & McCabe, 1989).

As noted, toward the end of the stimuli exposure periods, BP was already elevated. What can explain this elevation in BP? Expectations regarding the onset time of a stimulus during a task have been shown to affect participants' psychophysiological responses and performance (Jennings, van der Molen & Terezis, 1987; Jennings, van der Molen, & Steinhauer, 1998; Van der Molen, Somsen, Jennings, Nieuwboer, & Orlebeke, 1987). In our study, the length of the stimulation blocks was identical throughout the experiment. Therefore, participants may have anticipated when the stimuli exposure period was about to end. The elevation in BP may thus point to the involvement of psychological factors, such as tension relief and/or decline in alertness following anticipation of the end of the stimuli exposure period, when recruitment of attention resources is lower (i.e., relief reflected in the autonomic reaction). An alternative explanation is that participants became habituated after being shown several pictures with similar valence (Breiter et al., 1996; Britton, Shin, Barrett, Rauch, & Wright, 2008; Denny et al., 2013; Fischer, Furmark, Wik, & Fredrikson, 2000; Ishai, Pessoa, Bikle, & Ungerleider, 2004; Phan, Wager, Taylor, & Liberzon, 2002; Wright et al., 2001).

Which physiological mechanisms can explain this BP reaction? BP is controlled by central autonomic influence over the baroreceptive system. Central control "top-down" inputs stem from the hypothalamus, amygdala and parabrachial nucleus and are directed to the nucleus of the solitary tract, which in turn influences the baroreceptive system and leads to changes in autonomic reactions related to motor behavior as well as defensive behavior and psychological stress (King, Menon, Hachinski, & Cechetto, 1999; Nowak et al., 1999; Oppenheimer, Gelb, Girvin, & Hachinski, 1992; Ruggiero, Mraovitch, Granata, Anwar, & Reis, 1987; Williamson, McColl, Mathews, Ginsburg, & Mitchell, 1999; Williamson et al., 2001, 2002; Yasui, Breder, Safer, & Cechetto, 1991). The nucleus of the solitary tract also plays a modulatory "bottom-up" role by influencing the activity of the periaqueductal gray, amygdala and hypothalamus and leading to an inhibition effect (Benarroch, 2008; Raven, 2008). It is possible that attention-related prefrontal–parietal networks influence the central autonomic control, either via input to the amygdala or to other regions.

Indeed, evidence shows that central aortic and peripheral BP measures are related to cognitive functions (Pase et al., 2013) and attention (Okon-Singer et al., 2014). Okon-Singer et al. (2014) manipulated attention to distracting and highly aversive pictures while simultaneously measuring neural activation using fMRI and peripheral BP. The results demonstrated that among healthy individuals, neurocognitive attention mechanisms modulate BP and neural reactions to aversive stimuli in a network that includes prefrontal, parietal, limbic and brainstem regions previously shown to be related both to emotion control and to BP reactivity. Gupta (2016) suggested that the decline in BP levels shown by Okon-Singer et al. (2014) is due to activation of feedback mechanisms in brain regions associated with emotional processing (Gupta, 2016). In our study, similar mechanisms may have caused the BP decrease in response to negative-valenced pictures. Further studies that combine measurement of neural activation, baroreceptive functioning and continuous peripheral BP may shed light on the mechanisms that mediate central control over BP reactivity in emotional tasks.

Despite the general similarities between the two experiments in pattern reactivity and relation with HR for both systolic and diastolic BP, differences in the experiments' time course were still observed in our study. A possible explanation for these differences may be that when stimuli are presented for a prolonged period of time, additional or different psychophysiological mechanisms come into play. In order to better understand the effect of stimuli presentation duration on BP response, further research is needed.

Moreover, the differences in BP reaction found in both experiments are relatively small. Nevertheless, these differences are significant and consistent with other findings in the field (Gianaros et al., 2005, 2012, 2008, 2009, 2017). For example, a recent study found relatively small differences between baseline BP levels and BP levels during stress-eliciting tasks, which also correlated with brain activity in areas related to psychological stressor processing and cardiovascular response (Gianaros et al., 2017).

In conclusion, to the best of our knowledge, this study is the first to directly compare continuous BP reactions to negative-valenced and neutral pictures. Employing advanced continuous measurement and analysis approaches, we found a decline in BP response to mild aversive stimuli, followed by a sharp increase in BP toward the end of the stimulation, which could not have been reveled using "classical" measurement and analysis techniques. We believe this pattern of response reflects the recruitment of expectation and attention mechanisms. Developing a second-to-second model of BP reactivity in a normative population may serve as a reference point for examining populations at cardiovascular risk relative to their emotional response.

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REFERENCES

Azbel-Jackson, L., Butler, L. T., Ellis, J. A., & Van Reekum, C. M. (2016). Stay calm! Regulating emotional responses by implementation intentions: Assessing the impact on physiological and subjective arousal. *Cognition and Emotion*, *30*(6), 1107–1121. https://doi.org/10.1080/02699931.2015.1049515

Baruch, M., Kwon, K. W., Abdel-Rahman, E., & Isaacs, R. (2007). The structure of the radial pulse-a novel noninvasive ambulatory blood pressure device. In J. D. Westwood, R. S. Haluck, & H. M. Hoffman (Eds.), *Medicine meets virtual reality 15: In vivo, in vitro, in silico: Designing the next in medicine* (pp. 40–42). Amsterdam, Netherlands: IOS Press.

Baruch, M. C., Warburton, D. E., Bredin, S. S., Cote, A., Gerdt, D. W., & Adkins, C. M. (2011). Pulse decomposition analysis of the digital arterial pulse during hemorrhage simulation. *Nonlinear Biomedical Physics*, *5*(1), 1. https://doi.org/10.1186/1753-4631-5-1

Benarroch, E. E. (2008). The arterial baroreflex: Functional organization and involvement in neurologic disease. *Neurology*, *71*(21), 1733–1738. https://doi.org/10.1212/01.wnl.0000335246.93495.92

Benjamini, Y., & Yekutieli, D. (2001). The control of the false discovery rate in multiple testing under dependency. *Annals of Statistics*, *29*(4), 1165–1188, https://doi.org/10.1214/aos/1013699998

Bohus, B., Benus, R., Fokkema, D., Koolhaas, J., Nyakas, C., Van Oortmerssen, G., … Steffens, A. (1987). Neuroendocrine states and behavioral and physiological stress responses. *Progress in Brain Research*, 57–70. Elsevier. https://doi.org/10.1016/S0079-6123(08)60196-X

Breiter, H. C., Etcoff, N. L., Whalen, P. J., Kennedy, W. A., Rauch, S. L., Buckner, R. L., … Rosen, B. R. (1996). Response and habituation of the human amygdala during visual processing of facial expression. *Neuron*, *17*(5), 875–887. https://doi.org/10.1016/S0896-6273(00)80219-6

Britton, J. C., Shin, L. M., Barrett, L. F., Rauch, S. L., & Wright, C. I. (2008). Amygdala and fusiform gyrus temporal dynamics: Responses to negative facial expressions. *BMC Neuroscience*, *9*(1), 44. https://doi.org/10.1186/1471-2202-9-44

Chobanian, A. V., Bakris, G. L., Black, H. R., Cushman, W. C., Green, L. A., Izzo, J. L. Jr, … Wright, J. T. Jr (2003). The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: The JNC 7 report. *JAMA*, *289*(19), 2560–2571. https://doi.org/10.1001/jama.289.19.2560

Chung, E., Chen, G., Alexander, B., & Cannesson, M. (2013). Non-invasive continuous blood pressure monitoring: A review of current applications. *Frontiers of Medicine*, *7*(1), 91–101. https://doi.org/10.1007/s11684-013-0239-5

Codispoti, M., Ferrari, V., & Bradley, M. M. (2006). Repetitive picture processing: Autonomic and cortical correlates. *Brain Research*, *1068*(1), 213–220. https://doi.org/10.1016/j.brainres.2005.11.009

Currie, I., & Durban, M. (2002). Flexible smoothing with P-splines: A unified approach. *Statistical Modelling*, *2*(4), 333–349. https://doi.org/10.1191/1471082x02st039ob

Dampney, R., Horiuchi, J., Tagawa, T., Fontes, M., Potts, P., & Polson, J. (2003). Medullary and supramedullary mechanisms regulating sympathetic vasomotor tone. *Acta Physiologica Scandinavica*, *177*(3), 209–218. https://doi.org/10.1046/j.1365-201X.2003.01070.x

Dan-Glauser, E. S., & Gross, J. J. (2011). The temporal dynamics of two response-focused forms of emotion regulation: Experiential, expressive, and autonomic consequences. *Psychophysiology*, *48*(9), 1309–1322. https://doi.org/10.1111/j.1469-8986.2011.01191.x

Denny, B. T., Fan, J., Liu, X., Guerreri, S., Mayson, S. J., Rimsky, L., … Koenigsberg, H. W. (2013). Insula–amygdala functional connectivity is correlated with habituation to repeated negative images. *Social Cognitive and Affective Neuroscience*, *9*(11), 1660–1667. https://doi.org/10.1093/scan/nst160

Deter, H., Blecher, A., & Weber, C. S. (2007). Cardiovascular reactivity of patients with essential and renal hypertension in an emotion-triggering interview. *Behavioral Medicine*, *32*(4), 117–125. https://doi.org/10.3200/BMED.32.4.117-125

Deter, H., Micus, C., Wagner, M., Sharma, A. M., & Buchholz, K. (2006). Salt sensitivity, anxiety, and irritability predict blood pressure increase over five years in healthy males. *Clinical and Experimental Hypertension*, *28*(1), 17–27. https://doi.org/10.1080/10641960500386627

Dimberg, U., Hansson, G. Ö., & Thunberg, M. (1998). Fear of snakes and facial reactions: A case of rapid emotional responding. *Scandinavian Journal of Psychology*, *39*(2), 75–80. https://doi.org/10.1111/1467-9450.00059

Eilers, P. H., & Marx, B. D. (1996). Flexible smoothing with B-splines and penalties. *Statistical Science*, *11*(2), 89–102. https://doi.org/10.1214/ss/1038425655

Fischer, H., Furmark, T., Wik, G., & Fredrikson, M. (2000). Brain representation of habituation to repeated complex visual stimulation studied with PET. *NeuroReport*, *11*(1), 123–126. https://doi.org/10.1097/00001756-200001170-00024

Fortin, J., Habenbacher, W., Gruellenberger, R., Wach, P., & Skrabal, F. (1998). Real-time monitor for hemodynamic beat-to-beat parameters and power spectra analysis of the biosignals. Paper presented at the Proceedings of the 20th Annual International Conference of the IEEE Engineering in Medicine and Biology Society. Vol. 20 Biomedical Engineering Towards the Year 2000 and Beyond (Cat. no. 98CH36286), 360–363. Hong Kong, China: IEEE.

Fortin, J., Habenbacher, W., Heller, A., Hacker, A., Grüllenberger, R., Innerhofer, J., … Wach, P. (2006). Non-invasive beat-to-beat cardiac output monitoring by an improved method of transthoracic bioimpedance measurement. *Computers in Biology and Medicine*, *36*(11), 1185–1203. https://doi.org/10.1016/j.compbiomed.2005.06.001

Fortin, J., Marte, W., Grüllenberger, R., Hacker, A., Habenbacher, W., Heller, A., … Skrabal, F. (2006). Continuous non-invasive blood pressure monitoring using concentrically interlocking control loops. *Computers in Biology and Medicine*, *36*(9), 941–957. https://doi.org/10.1016/j.compbiomed.2005.04.003

Garfinkel, S. N., Zorab, E., Navaratnam, N., Engels, M., Mallorqui-Bague, N., Minati, L., … Critchley, H. D. (2016). Anger in brain and body: The neural and physiological perturbation of decision-making by emotion. *Social Cognitive and Affective Neuroscience*, *11*(1), 150–158. https://doi.org/10.1093/scan/nsv099

Gerin, W., Davidson, K. W., Christenfeld, N. J., Goyal, T., & Schwartz, J. E. (2006). The role of angry rumination and distraction in blood pressure recovery from emotional arousal. *Psychosomatic Medicine*, *68*(1), 64–72. https://doi.org/10.1097/01.psy.0000195747.12404.aa

Gianaros, P. J., Derbtshire, S. W., May, J. C., Siegle, G. J., Gamalo, M. A., & Jennings, J. R. (2005). Anterior cingulate activity correlates with blood pressure during stress. *Psychophysiology*, *42*(6), 627–635. https://doi.org/10.1111/j.1469-8986.2005.00366.x

Gianaros, P. J., Jennings, J. R., Sheu, L. K., Derbyshire, S. W., & Matthews, K. A. (2007). Heightened functional neural activation to psychological stress covaries with exaggerated blood pressure reactivity. *Hypertension*, *49*(1), 134–140. https://doi.org/10.1161/01.HYP.0000250984.14992.64

Gianaros, P. J., Onyewuenyi, I. C., Sheu, L. K., Christie, I. C., & Critchley, H. D. (2012). Brain systems for baroreflex suppression during stress in humans. *Human Brain Mapping*, *33*(7), 1700–1716. https://doi.org/10.1002/hbm.21315

Gianaros, P. J., & Sheu, L. K. (2009). A review of neuroimaging studies of stressor-evoked blood pressure reactivity: Emerging evidence for a brain-body pathway to coronary heart disease risk. *NeuroImage*, *47*(3), 922–936. https://doi.org/10.1016/j.neuroimage.2009.04.073

Gianaros, P. J., Sheu, L. K., Matthews, K. A., Jennings, J. R., Manuck, S. B., & Hariri, A. R. (2008). Individual differences in stressor-evoked blood pressure reactivity vary with activation, volume, and functional connectivity of the amygdala. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*, *28*(4), 990–999. https://doi.org/10.1523/JNEUROSCI.3606-07.2008

Gianaros, P. J., Sheu, L. K., Remo, A. M., Christie, I. C., Crtichley, H. D., & Wang, J. (2009). Heightened resting neural activity predicts exaggerated stressor-evoked blood pressure reactivity. *Hypertension*, *53*(5), 819–825. https://doi.org/10.1161/HYPERTENSIONAHA.108.126227

Gianaros, P. J., Sheu, L. K., Uyar, F., Koushik, J., Jennings, J. R., Wager, T. D., … Verstynen, T. D. (2017). A brain phenotype for stressor-evoked blood pressure reactivity. *Journal of the American Heart Association*, *6*(9), e006053. https://doi.org/10.1161/JAHA.117.006053

Grassi, G., & Esler, M. (2002). The sympathetic nervous system in renovascular hypertension: Lead actor or 'bit'player? *Journal of Hypertension*, *20*(6), 1071–1073. https://doi.org/10.1097/00004872-200206000-00013

Gray, M. A., Rylander, K., Harrison, N. A., Wallin, B. G., & Critchley, H. D. (2009). Following one's heart: Cardiac rhythms gate central initiation of sympathetic reflexes. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*, *29*(6), 1817–1825. https://doi.org/10.1523/JNEUROSCI.3363-08.2009

Grubbs, F. E. (1950). Sample criteria for testing outlying observations. *The Annals of Mathematical Statistics*, *21*(1), 27–58. https://doi.org/10.1214/aoms/1177729885

Gupta, R. (2016). Commentary: Neural control of vascular reactions: Impact of emotion and attention. *Frontiers in Psychology*, *7*, 1613. https://doi.org/10.1523/JNEUROSCI.0747-13.2014

Hamaker, E. L., van Hattum, P., Kuiper, R. M., & Hoijtink, H. (2011). Model selection based on information criteria in multilevel modeling. In J. Hox & J. K. Roberts (Eds.), *Handbook of advanced multilevel analysis* (pp. 231–255). New York, NY, US: Routledge.

Harris, C. R., & Pashler, H. (2004). Attention and the processing of emotional words and names: Not so special after all. *Psychological Science*, *15*(3), 171–178. https://doi.org/10.1111/j.0956-7976.2004.01503005.x

Hennig, A., & Patzak, A. (2013). Continuous blood pressure measurement using pulse transit time. *Somnologie-Schlafforschung Und Schlafmedizin*, *17*(2), 104–110. https://doi.org/10.1007/s11818-013-0617-x

Ishai, A., Pessoa, L., Bikle, P. C., & Ungerleider, L. G. (2004). Repetition suppression of faces is modulated by emotion. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(26), 9827–9832. https://doi.org/10.1073/pnas.0403559101

Jeleazcov, C., Krajinovic, L., Münster, T., Birkholz, T., Fried, R., Schüttler, J., & Fechner, J. (2010). Precision and accuracy of a new device (CNAP™) for continuous non-invasive arterial pressure monitoring: Assessment during general anaesthesia. *British Journal of Anaesthesia*, *105*(3), 264–272. https://doi.org/10.1093/bja/aeq143

Jennings, J. R., van der Molen, M. W., & Terezis, C. (1987). Primary bradycardia and vagal inhibition as two manifestations of the timing of vagal influence on the heart beat. *Journal of Psychophysiology*, *1*(4), 361–374.

Jennings, J. R., Kamarck, T. W., Everson-Rose, S. A., Kaplan, G. A., Manuck, S. B., & Salonen, J. T. (2004). Exaggerated blood pressure responses during mental stress are prospectively related to enhanced carotid atherosclerosis in middle-aged finnish men. *Circulation*, *110*(15), 2198–2203. 1010.1161/01.CIR.0000143840.77061.E9.

Jennings, J. R., van der Molen, M. W., & Steinhauer, S. R. (1998). Preparing the heart, eye, and brain: Foreperiod length effects in a nonaging paradigm. *Psychophysiology*, *35*(1), 90–98. https://doi.org/10.1111/1469-8986.3510090

King, A. B., Menon, R. S., Hachinski, V., & Cechetto, D. F. (1999). Human forebrain activation by visceral stimuli. *Journal of Comparative Neurology*, *413*(4), 572–582. https://doi.org/10.1002/(SICI)1096-9861(19991101)413:4<572:AID-CNE6>3.0.CO;2-S

Lacey, B. C., & Lacey, J. I. (1974). Studies of heart rate and other bodily processes in sensorimotor behavior. In P. A. Obrist, A. H. Black, J. Brener, & L. V. DiCara (Eds.), *Cardiovascular psychophysiology: Current issues in response mechanisms, biofeedback and methodology* (pp. 538–564). Chicago, IL: AldineTransaction.

Lacey, B. C., & Lacey, J. I. (1978). Two-way communication between the heart and the brain: Significance of time within the cardiac cycle. *American Psychologist*, *33*(2), 99. https://doi.org/10.1037/0003-066X.33.2.99

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (2008). *International affective picture system (IAPS): Affective ratings of pictures and instruction manual*. Gainesville: University of Florida.

Lang, P. J., Davis, M., & Öhman, A. (2000). Fear and anxiety: Animal models and human cognitive psychophysiology. *Journal of Affective Disorders*, *61*(3), 137–159. https://doi.org/10.1016/S0165-0327(00)00343-8

Lang, P. J., Greenwald, M. K., Bradley, M. M., & Hamm, A. O. (1993). Looking at pictures: Affective, facial, visceral, and behavioral reactions. *Psychophysiology*, *30*(3), 261–273. https://doi.org/10.1111/j.1469-8986.1993.tb03352.x

Lee, E. T. (1982). A simplified B-spline computation routine. *Computing*, *29*(4), 365–371. https://doi.org/10.1007/BF02246763

Lehrer, P. M., Hochron, S., Carr, R., Edelberg, R., Hamer, R., Jackson, A., & Porges, S. (1996). Behavioral task-induced bronchodilation in asthma during active and passive tasks: A possible cholinergic link to psychologically induced airway changes. *Psychosomatic Medicine*, *58*(5), 413–422. https://doi.org/10.1097/00006842-199609000-00004

Lohmeier, T. E., Dwyer, T. M., Hildebrandt, D. A., Irwin, E. D., Rossing, M. A., Serdar, D. J., & Kieval, R. S. (2005). Influence of prolonged

baroreflex activation on arterial pressure in angiotensin hypertension. *Hypertension*, *46*(5), 1194–1200. https://doi.org/10.1161/01.HYP.0000187011.44201.2e

Lohmeier, T. E., Dwyer, T. M., Irwin, E. D., Rossing, M. A., & Kieval, R. S. (2007). Prolonged activation of the baroreflex abolishes obesity-induced hypertension. *Hypertension*, *49*(6), 1307–1314. https://doi.org/10.1161/HYPERTENSIONAHA.107.087874

Matthews, K. A., Katholi, C. R., McCreath, H., Whooley, M. A., Williams, D. R., Zhu, S., & Markovitz, J. H. (2004). Blood pressure reactivity to psychological stress predicts hypertension in the CARDIA study. *Circulation*, *110*(1), 74–78. https://doi.org/10.1161/01.CIR.0000133415.37578.E4

McCubbin, J. A., Merritt, M. M., Sollers, J. J. 3rd, Evans, M. K., Zonderman, A. B., Lane, R. D., & Thayer, J. F. (2011). Cardiovascular-emotional dampening: The relationship between blood pressure and recognition of emotion. *Psychosomatic Medicine*, *73*(9), 743–750. https://doi.org/10.1097/PSY.0b013e318235ed55

Nakagawa, S., & Schielzeth, H. (2013). A general and simple method for obtaining R2 from generalized linear mixed-effects models. *Methods in Ecology and Evolution*, *4*(2), 133–142. https://doi.org/10.1111/j.2041-210x.2012.00261.x

Nowak, M., Olsen, K. S., Law, I., Holm, S., Paulson, O. B., & Secher, N. H. (1999). Command-related distribution of regional cerebral blood flow during attempted handgrip. *Journal of Applied Physiology*, *86*(3), 819–824. https://doi.org/10.1152/jappl.1999.86.3.819

Okon-Singer, H., Mehnert, J., Hoyer, J., Hellrung, L., Schaare, H. L., Dukart, J., & Villringer, A. (2014). Neural control of vascular reactions: Impact of emotion and attention. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*, *34*(12), 4251–4259. https://doi.org/10.1523/JNEUROSCI.0747-13.2014

Okon-Singer, H., Mehnert, J., Hoyer, J., Hellrung, L., Schaare, H. L., Dukart, J., & Villringer, A. (2016). Commentary: Neural control of vascular reactions: Impact of emotion and attention. *Frontiers in Psychology*, *7*, 1613. https://doi.org/10.1523/JNEUROSCI.0747-13.2014

Oppenheimer, S. M., Gelb, A., Girvin, J. P., & Hachinski, V. C. (1992). Cardiovascular effects of human insular cortex stimulation. *Neurology*, *42*(9), 1727–1727. https://doi.org/10.1212/WNL.42.9.1727

Pase, M. P., Stough, C., Grima, N. A., Harris, E., Macpherson, H., Scholey, A. B., & Pipingas, A. (2013). Blood pressure and cognitive function: The role of central aortic and brachial pressures. *Psychological Science*, *24*(11), 2173–2181. https://doi.org/10.1177/0956797613488602

Phan, K. L., Wager, T., Taylor, S. F., & Liberzon, I. (2002). Functional neuroanatomy of emotion: A meta-analysis of emotion activation studies in PET and fMRI. *NeuroImage*, *16*(2), 331–348. https://doi.org/10.1006/nimg.2002.1087

Pury, C. L., McCubbin, J. A., Helfer, S. G., Galloway, C., & McMullen, L. J. (2004). Elevated resting blood pressure and dampened emotional response. *Psychosomatic Medicine*, *66*(4), 583–587. https://doi.org/10.1097/01.psy.0000130490.57706.88

Raven, P. (2008). Recent advances in baroreflex control of blood pressure during exercise in humans: An overview. *Medicine Science in Sports Exercise*, *40*(12), 2033. https://doi.org/10.1097/01.psy.0000130490.57706.88

Ruggiero, D. A., Mraovitch, S., Granata, A. R., Anwar, M., & Reis, D. J. (1987). A role of insular cortex in cardiovascular function. *Journal of Comparative Neurology*, *257*(2), 189–207. https://doi.org/10.1002/cne.902570206

Sacco, R. L., Wolf, P. A., & Gorelick, P. B. (1999). Risk factors and their management for stroke prevention: Outlook for 1999 and beyond. *Neurology*, *53*(7 Suppl 4), S15–S24.

Schneiderman, N., & McCabe, P. M. (1989). Psychophysiologic strategies in laboratory research. In N. Schneiderman, S. M. Weiss, & P. G. Kaufmann (Eds.), *Handbook of research methods in cardiovascular behavioral medicine* (pp. 349–364). Boston, MA, US: Springer.

Schwarz, G. (1978). Estimating the dimension of a model. *The Annals of Statistics*, *6*(2), 461–464. https://doi.org/10.1214/aos/1176344136

Shapiro, D., Greenstadt, L., Lane, J. D., & Rubinstein, E. (1981). Tracking-cuff system for beat-to-beat recording of blood pressure. *Psychophysiology*, *18*(2), 129–136. https://doi.org/10.1111/j.1469-8986.1981.tb02926.x

Shiyko, M. P., Lanza, S. T., Tan, X., Li, R., & Shiffman, S. (2012). Using the time-varying effect model (TVEM) to examine dynamic associations between negative affect and self confidence on smoking urges: Differences between successful quitters and relapsers. *Prevention Science*, *13*(3), 288–299. https://doi.org/10.1007/s11121-011-0264-z

Tooley, M. D., Carmel, D., Chapman, A., & Grimshaw, G. M. (2017). Dissociating the physiological components of unconscious emotional responses. *Neuroscience of Consciousness*, *3*(1), nix021. https://doi.org/10.1093/nc/nix021

Treiber, F. A., Kamarck, T., Schneiderman, N., Sheffield, D., Kapuku, G., & Taylor, T. (2003). Cardiovascular reactivity and development of preclinical and clinical disease states. *Psychosomatic Medicine*, *65*(1), 46–62. https://doi.org/10.1097/00006842-200301000-00007

Ugajin, T., Hozawa, A., Ohkubo, T., Asayama, K., Kikuya, M., Obara, T., … Imai, Y. (2005). White-coat hypertension as a risk factor for the development of home hypertension: The ohasama study. *Archives of Internal Medicine*, *165*(13), 1541–1546. https://doi.org/10.1001/archinte.165.13.1541

van der Molen, M. W., Somsen, R. J., Jennings, J. R., Nieuwboer, R., & Orlebeke, J. F. (1987). A psychophysiological investigation of cognitive-energetic relations in human information processing: A heart rate/additive factors approach. *Acta Psychologica*, *66*(3), 251–289. https://doi.org/10.1016/0001-6918(87)90039-4

Wagenmakers, E. (2007). A practical solution to the pervasive problems ofp values. *Psychonomic Bulletin & Review*, *14*(5), 779–804. https://doi.org/10.3758/BF03194105

Wangelin, B. C., Löw, A., McTeague, L. M., Bradley, M. M., & Lang, P. J. (2011). Aversive picture processing: Effects of a concurrent task on sustained defensive system engagement. *Psychophysiology*, *48*(1), 112–116. https://doi.org/10.1111/j.1469-8986.2010.01041.x

Williamson, J., McColl, R., Mathews, D., Ginsburg, M., & Mitchell, J. (1999). Activation of the insular cortex is affected by the intensity of exercise. *Journal of Applied Physiology*, *87*(3), 1213–1219. https://doi.org/10.1152/jappl.1999.87.3.1213

Williamson, J., McColl, R., Mathews, D., Mitchell, J., Raven, P., & Morgan, W. (2001). Hypnotic manipulation of effort sense during dynamic exercise: Cardiovascular responses and brain activation. *Journal of Applied Physiology*, *90*(4), 1392–1399. https://doi.org/10.1152/jappl.2001.90.4.1392

Williamson, J., McColl, R., Mathews, D., Mitchell, J., Raven, P., & Morgan, W. (2002). Brain activation by central command during actual and imagined handgrip under hypnosis. *Journal of Applied Physiology*, *92*(3), 1317–1324. https://doi.org/10.1152/japplphysiol.00939.2001

Wright, C. I., Fischer, H., Whalen, P. J., McInerney, S. C., Shin, L. M., & Rauch, S. L. (2001). Differential prefrontal cortex and amygdala habituation to repeatedly presented emotional stimuli. *Neuroreport*, *12*(2), 379–383. https://doi.org/10.1097/00001756-200102120-00039

Yan, L. L., Liu, K., Matthews, K. A., Daviglus, M. L., Ferguson, T. F., & Kiefe, C. I. (2003). Psychosocial factors and risk of hypertension: The coronary artery risk development in young adults (CARDIA) study. *JAMA*, *290*(16), 2138–2148. 1010.1001/jama.290.16.2138.

Yasui, Y., Breder, C. D., Safer, C. B., & Cechetto, D. F. (1991). Autonomic responses and efferent pathways from the insular cortex in the rat. *Journal of Comparative Neurology*, *303*(3), 355–374. https://doi.org/10.1002/cne.903030303

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Table 1: A model describing systolic BP based on Experiment 1, with parameter estimates for fixed and random effects, effect size (marginal R2) and model fit (x2/DF).
Table 2: A model describing diastolic BP based on Experiment 1, with parameter estimates for fixed and random effects, effect size (marginal R2) and model fit (x2/DF).
Table 3: A model describing HR based on Experiment 1, with parameter estimates for fixed and random effects, effect size (marginal R2) and model fit (x2/DF).
Table 4: A model describing systolic BP based on Experiment 2, with parameter estimates for fixed and random effects, effect size (marginal R2) and model fit (x2/DF).
Table 5: A model describing diastolic BP based on Experiment 2, with parameter estimates for fixed and random effects, effect size (marginal R2) and model fit (x2/DF).
Table 6: A model describing HR based on Experiment 2, with parameter estimates for fixed and random effects, effect size (marginal R2) and model fit (x2/DF).

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