Original Article

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Abnormalities in emotional and motor reactions among young prehypertensive individuals: employing continuous blood pressure analysis

Avigail Wiener[a,b], Pavel Goldstein[c], Keren Doenyas[d,e], and Hadas Okon-Singer[a,b]

Background: Essential hypertension is an important risk factor for cerebrovascular diseases and a major cause of premature death in industrialized societies. A predisposing factor for essential hypertension is prehypertension: blood pressure (BP) values at rest that are at the higher end of the normal range. Abnormally enhanced cardiovascular responses to motor and emotional tasks have been found as predictors of essential hypertension. Yet, knowledge regarding the BP reaction to aversive stimuli and motor reaction in prehypertension is limited.

Methods: We compared the reaction to aversive and neutral stimuli inducing an emotional response (experiment 1) and to the isometric handgrip exercise (IHE) inducing a motor response (experiment 2), between prehypertensive and normotensive controls. BP reactions were measured and analyzed in a continuous fashion, in contrast to previous studies that averaged BP responses across blocks. We applied a multilevel B-spline model, a continuous analysis that enabled a better understanding of the BP time course and the detection of subtle differences between groups.

Results: In both tasks, we found that prehypertensive individuals showed enhanced DBP reactions compared with normotensive controls; prehypertensive individuals exhibited lower BP responses to aversive pictures and higher BP responses to the IHE. These results are in line with previous studies with healthy or hypertensive participants and suggest abnormalities already in the prehypertensive stage.

Conclusion: Considering the high frequency and health risks related to prehypertension, understanding the autonomic reactions to emotional and motor stimuli in this population is of clinical and theoretical importance and could serve as a behavioural marker to identify at-risk groups.

Keywords: continuous analysis, continuous measurement, DBP, emotional reaction, motor reaction, prehypertension, SBP

Abbreviations: BP, blood pressure; HR, heart rate; IHE, isometric handgrip exercise

INTRODUCTION

Essential hypertension is a main risk factor for premature death and a huge burden on healthcare systems in Western societies [1–3]. essential hypertension affects half the population over the age of 55 years and often results in heart attack, stroke and dementia [4,5]. Available antihypertensive drugs alone are unsatisfactory treatment for essential hypertension [6]. Therefore, a call for a paradigm shift has been made, from treatment of manifest essential hypertension to prevention based on a risk-factor approach [1,4]. A well known important risk factor for essential hypertension defined by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) is prehypertension (BP values at rest ranging from 120/80 to 139/89 mmHg) [1,7,8]. Understanding possible abnormalities in prehypertension could enable deeper insight into the way essential hypertension is developed and the mechanisms involved in its early stages.

Abnormally enhanced cardiovascular responses to intensive physical exercise have been shown among prehypertensive individuals [9] and were found as predictors of essential hypertension [10–12]. A recent review also noted that people with exaggerated BP reactions to physical exercise typically have resting BP in the prehypertensive range [13]. The isometric handgrip exercise (IHE), commonly used to increase arterial pressure [14–19], resulted in enhanced arterial pressure, metaboreflex sensitivity and sympathetic responses in participants with essential hypertension compared with normotensive controls [15,17,19]. Offspring of hypertensive parents, a risk group for developing essential hypertension later in life, show larger elevation in BP levels in the IHE compared with participants with normotensive parents [16]. Initial evidence also showed exaggerated BP responses to IHE in prehypertensive compared with normotensive individuals. Note, however that this latter pilot study was based solely on six

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[a]Department of Psychology, School of Psychological Sciences, [b]The Integrated Brain and Behavior Research Center (IBBR), [c]School of Public Health, University of Haifa, [d]Department of Nephrology and Hypertension, Shamir Medical Center (Assaf Harofeh), Sackler School of Medicine, Tel Aviv University and [e]Sagol Center for Hyperbaric Medicine and Research, Shamir Medical Center (Assaf Harofeh), Tel Aviv, Israel

Correspondence to Avigail Wiener, Department of Psychology, University of Haifa, Israel. Tel: +972 4 8249671; e-mail: wieneravigail@gmail.com

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African American young adult women in each group [14] and should be replicated in a larger sample to draw firm conclusions.

Similarly to their exaggerated BP reactions to motor tasks, patients with essential hypertension and those at risk show enhanced BP reactions in response to stress and aversive situations [20–25]. There is also evidence for a decline in BP levels in response to attention demanding aversive stimuli among normotensive participants [26–29]. We [30] recently found an enhanced decline in peripheral BP when reacting to highly aversive pictures compared with neutral pictures among normotensive participants. Importantly, we employed an innovative continuous measurement and analysis technique, which detected subtle differences in BP fluctuations that were not discoverable by averaging the BP response over the whole experimental time course, as done in previous studies [22,28,31–33].

Knowledge regarding the BP reaction to aversive stimuli and the IHE in prehypertension is very limited. As prehypertension is a main risk factor for future development of essential hypertension, such knowledge is critical in developing efficient prevention strategies. Therefore, in the current study, we compared the reaction to negative stimuli (experiment 1) and the IHE (experiment 2) of prehypertensive and normotensive controls. By employing two different tasks, known to result in an opposite BP change direction (i.e. elevated BP reaction in the IHE and decreased BP in the emotional task), we were able to elucidate basic common mechanisms associated with enhanced BP reaction in prehypertension. Furthermore, existing studies on BP reaction to stress, motor tasks or emotional stimulation in prehypertension did not use continuous measurement and analysis, limiting their potential findings. As in our previous work, we measured BP continuously instead of averaging the BP reactions prestimulation and poststimulation.

The aim of the current study was to evaluate BP responses to motor and emotional tasks in prehypertensive individuals using a continuous measurement and analysis technique instead of averaging the BP measurements. On the basis of the previous findings in patients diagnosed with essential hypertension or having a genetic risk, we hypothesize abnormally enhanced reactions in prehypertensive individuals in both tasks, namely an abnormally larger BP decline in the emotional task and an elevated BP in the IHE task. The BP response in these tasks could help explain the mechanism underlying the expected enhanced response. An enhanced reaction only in the emotional task would suggest abnormal central regulation while an enhanced reaction only in the motor task could indicate abnormality in the vascular response. Additionally, heart rate (HR) was added to the analysis model in order to examine whether it can explain the BP reaction.

MATERIALS AND METHODS

Experiment 1: emotional blood pressure reaction

Experiment 1 was designed to compare the reaction to aversive vs. neutral pictures between prehypertensive individuals and normotensive controls.

Participants

Fifty students from the University of Haifa participated in the study, 25 normotensive (10 female students; BP at rest ranged from 90 to 119 mmHg systolic and 60–79 mmHg diastolic) and 25 prehypertensive participants according to the JNC-7 classifications [1] (8 women; BP at rest ranged from 120 to 139 mmHg systolic and 80–89 mmHg diastolic). (Please note that when conducting this study, these BP values were defined as prehypertension. According to the new guidelines, these values now refer to 'Elevated' and 'Stage 1 hypertension' according to American heart association [65] and 'Normal' and 'High normal' according to the European guidelines [66].)

Two BP measurements were taken on separate days within 1 week to ensure that only normotensives and prehypertensive individuals were included in the study [1]. On each day, participants' BP at rest was measured three times while they were in a seated position. Before the measurements were taken, participants rested in a seated position for 5 min. For all three measurements, participants sat on a comfortable chair with back support, with one hand resting on a table. The BP measurement cuff was placed above the elbow at heart level, as recommended by the manufacturer. Participants were instructed to place both feet on the ground and not to cross their legs. The three measurements lasted about 10 min, with about 3 min between each of the two subsequent measures. A mean BP level was calculated for all three measurements. A third verification BP measurement was taken on the day of the experiment, before the experiment began. Participants with mean resting SBP levels between 90 and 119 mmHg and DBP levels between 60 and 79 mmHg were assigned to the normotensive group; and participants with mean resting SBP levels between 120 and 139 mmHg and/or DBP levels between 80 and 89 mmHg were assigned to the prehypertensive group.

Additional inclusion criteria included participants aged between 18 and 35 years old and correct or corrected-to-normal vision. Exclusion criteria included history of substance abuse, neurologic diseases, psychiatric disorders, cardiovascular diseases or any other chronic diseases. Participants were also instructed to refrain from consuming caffeine, physical exercise and smoking 3 h prior to participating in the experiment. The study was approved by the local ethics committee (Approval Number 278/14) and all participants gave their informed consent before the beginning of the experiment. Data from the control participants who performed the exact same protocol was also included in another paper from our group [30].

Methods

Demographic and trait differences between groups

At the beginning of the experiment, participants reported their age and BMI values as well as their medical history. At the end of the experimental session, participants completed the STAI [34] and BDI-II [35] questionnaires to examine possible differences in anxiety and depression, respectively, between groups.

Stimuli

Eighty aversive (such as mutilated bodies, fear-evoking dangerous animals and body malformations) and 80 neutral pictures (such as still objects or food) from the International Affective Picture System [36] were chosen based on previous studies by our group [28], and based on valence ratings (aversive picture valence: mean: 2.35, SD: 0.84; neutral picture valence: mean: 5.13, SD: 0.51). The IAPS is a large set of standardized, ecological and emotionally evocative color photographs, covering a wide range of categories. Each picture was normatively rated in the United States in terms of valence (ranging from pleasant to unpleasant), arousal (ranging from calm to exciting) and dominance (ranging from 'in control' to dominant).

Experimental task

The experiment included 16 experimental blocks presented in randomized order. Each block included a 60-s stimuli exposure period constituting 10 trials with neutral pictures (i.e. a neutral block) or 10 trials with aversive pictures (i.e. aversive block), followed by 60 s of rest to allow BP to recover (Fig. 1a). Each trial started with a fixation cross shown for 1 s, followed by presentation of a picture at the centre of the screen for 5 s (Fig. 1b).

Continuous blood pressure measurement

Continuous peripheral BP (SBP, DBP and mean arterial BP) was recorded during the task via a noninvasive double finger cuff placed on the left index and middle fingers. Prior to the beginning of the task, beat-to-beat measurement from the finger was calibrated with an arterial cuff placed on right upper arm, while participants were in a seated position and their left arm was fixed at 90° on a table in front of them. Their right arm was placed on the armchair on which they were sitting on. No additional calibration accrued during the task. The arterial pulse signal was recorded using an NIBP100D-HD device (CareTaker unit, Empirical Technologies/Biopac Systems Inc., Goleta, California, USA; http://www.biopac.com). This device and procedure have been validated in previous studies [37–40] and were 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. Data were sampled at a 500 Hz sampling rate.

Continuous heart rate measurement

HR was continuously recorded during the task using standard three-lead ECG placement. The signal was sampled at a rate of 1000 Hz, with a high-pass filter of 0.5 Hz using a Biopac MP150 system (Biopac ECG module, Goleta, California, USA).

Procedure

After filling the consent form, participants were prepared for the physiological recordings and BP calibration. Participants were seated approximately 50 cm in front of a 23.7 inch computer screen. Participants sat on a comfortable arm-chair with back support. They were instructed to set both feet on the ground and not to cross legs. The BP measurement cuff was put above the elbow at heart level as recommended by the manufacturer. During calibration, both arms were placed on the table to verify a comfortable and stable position. During the experimental blocks, the arm with the finger cuff was fixated in a stable position on the table at heart level. They were then instructed to look at the screen throughout the experiment and freely watch the pictures that appeared on the screen. The task's length was approximately 40 min.

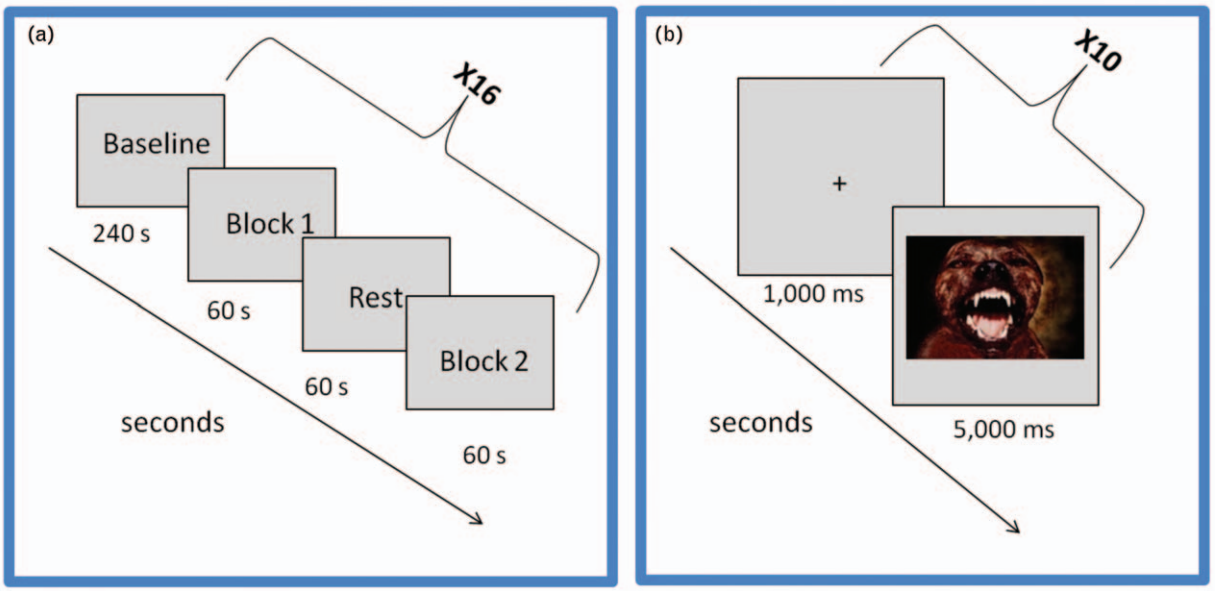

FIGURE 1 Experiment 1 design. (a) Experiment design: 16 blocks were presented, containing either neutral or aversive pictures in randomized order. Each block lasted 60 s, followed by 60 s of rest, resulting in a total of 40 min. Each block contained either neutral or aversive pictures. (b) Example of a trial depicting an aversive picture used in the experiment. Each trial began with a fixation cross shown for 1 s, followed by a picture presented for 5 s. Ten pictures were presented in each of the 16 experimental blocks.

Preprocessing and analysis

Demographic and trait differences between groups

Differences between groups in age, BMI, anxiety, depression and BDI were analyzed using independent *t* tests performed with SPSS software (version 20, http://www-01.ibm.com/software/analytics/spss).

Blood pressure and heart rate data preprocessing

Visual inspection for artefacts was followed by the Grubbs' test to detect outliers (Grubbs, 1950). BP peaks were removed if they exceeded 0.3–1.3 s between intervals of the systolic/diastolic peaks. The HR data were cleaned using the same method. Similarly to our previous study [30], the first stimulus in each block (i.e. 5 s measured from the presentation of the first picture) was removed to avoid additional artifacts. In addition, because of a large variance that affected model convergence, we removed the last 10 s of the recovery period.

For each block, a specific baseline was calculated by averaging the BP during the 5 s prior to the presentation of the first picture in this block. This baseline was subtracted from the BP at each time point during the block and recovery periods. These values were entered in the B-spline mixed-model.

Blood pressure data analysis

A multilevel B-spline model was implemented to assess group differences in BP reactions as a function of the time course during the block. The model tested the three-way interaction between group (normotensives/prehypertensive individuals), picture valence (aversive/neutral) and B-spline time. We tested different model structures that varied by the residuals' distribution [Gaussian, number of B-spline knots (2–5)] and its form (linear, quadratic, cubic) and included random effects. Model fit was estimated using the Bayesian Information Criteria (BIC) [41,42], whereby the model with the best fit shows the minimal BIC. Model fit was assessed by a change in BIC, reported in ΔBIC, calculated as the BIC of the interaction model − the BIC of the model without interaction. According to previous studies, relying only on *P* values for multilevel models is problematic [41,43]. Therefore, we used ΔBIC as a second criterion for model quality. According to our decision rule, only when the parameter of interest was significant ($P < 0.05$) and the ΔBIC indicated an improvement in the model, did we consider the result to be significant. Finally, the effect size of the model was assessed by calculating marginal R^2 based on Nakagawa and Schielzeth [44]. The model with the best fit was based on Gaussian residuals and included four knots with cubic spline, random intercept and random B-spline time effects for participants and blocks, nested into the participants that differentiated between the experimental conditions.

To understand this three-way interaction between group, valence and B-spline time, we examined the two-way interaction between group and valence at each time point of the block and recovery period. Then, for the time points in which the two-way interaction was significant, we further examined the differences in reactions to aversive and neutral pictures using model-based contrasts with false discovery rate (FDR) correction for the dependent set of tests [45]. Additional analyses focused on comparison of the groups' slopes and minimum point BP levels reached during the stimulus exposure period. Further details are presented in the supplementary material, http://links.lww.com/HJH/B653.

In addition, as the number of male and female participants was not similar, we ran the B-spline model again while correcting for gender.

Finally, HR was added as an additional predictor to the same model in order to test the associations between HR and BP taking into account the study design. Separate models were used for SBP and DBP.

Experiment 2: isometric handgrip exercise

Experiment 1 established the measurement and analysis of continuous BP among prehypertensive participants. Following, experiment 2 examined a different sample of participants and focused on potential differences between prehypertensives and normotensive controls in motor reactions, as demonstrated by the IHE.

Participants

Fifty-seven students from the University of Haifa and the Technion – Israel Institute of Technology participated in the study in return for payment or course credit, 28 normotensive (5 female participants) and 29 prehypertensive individuals (7 female participants). All other participant characteristics met the same criteria as in experiment 1.

Measures

Procedure

All procedures prior to the task were similar to Experiment 1.

Isometric handgrip exercise

The task began with a 1 min initial rest period, followed by 10 identical consecutive blocks. Each block was divided into two periods: an exercise period and a resting period. The exercise period started with a fixation cross shown for 500 ms followed by presenting the word 'press' at the centre of the screen for 15 s, signalling to participants to press down on the handgrip spring dynamometer in their right hand, with all their strength as many times as possible. Afterwards the resting period began by presenting the word 'rest' at the centre of the screen for 30 s, signalling to participants to release the handgrip and relax (Fig. 4).

Data preprocessing and analysis

Preprocessing was similar to experiment 1. Data analysis was based on a B-spline model including the two-way interaction between groups (normotensives/prehypertensive individuals) and B-spline-transformed time. To understand this interaction, we examined the differences in BP reactions at each second during the IHE as well as during the resting periods, applying FDR correction for the dependent set of tests [45]. Similar to experiment 1, the

model fit was assessed by a change in BIC, reported in ΔBIC. Additional analyses focused on comparison of the slopes and maximum point BP levels reached from 5 s after block onset to the maximum point during the 15 s of the IHE period (see supplementary material, http://links.lww.com/HJH/B653). In addition, as in experiment 1, we further ran the B-spline model while correcting for gender and added HR as an additional predictor in separate models for SBP and DBP, in order to examine the associations of BP and HR.

RESULTS

Experiment 1: emotional blood pressure reaction

Demographic differences between groups

As shown in Table 1, participants did not differ in age, BMI, anxiety or depression levels (all Ps > 0.05). As expected, participants' mean SBP and DBP measures, taken before the beginning of the experiment, differed between groups.

Blood pressure differences between the groups

DBP reactivity

The multilevel B-spline model revealed a three-way interaction between group (normotensive/prehypertensive), valence (aversive/negative) and time ($F(28,672) = 7.34$, $P < 0.0001$, $\Delta BIC = 262.4$). Further analyses to explain this three-way interaction focused on the differences between valence and groups at every second during the stimulus exposure and recovery periods (see Fig. 2). Indeed, the pattern of DBP reactions differed significantly between groups and the valence during large parts of the stimulus exposure and recovery periods (for details, see the supplementary material, http://links.lww.com/HJH/B653). Although both groups' reactions were a decline in BP in response to aversive compared with neutral pictures (all Ps < 0.05), this decrease was larger in the prehypertensive compared with the normotensive group. In addition, a slower recovery back to baseline in response to aversive compared with neutral pictures was found only in the prehypertensive group (all Ps < 0.05).

In addition, controlling for gender did not change any of the effects or their pattern. Hence, gender had no effect on the findings.

SBP reactivity

The multilevel B-spline model revealed a three-way interaction between group, valence and time ($F(28,672) = 9.2$, $P < 0.0001$, $\Delta BIC = 374.1$). Similar to the DBP, further analyses to explain this three-way interaction focused on the differences between valence and groups at every second during the stimulus exposure and recovery periods (see Fig. 3). Again, the pattern of SBP reaction differed significantly between groups and valence during large parts of the stimulus exposure and recovery periods (for details, see the supplementary material, http://links.lww.com/HJH/B653). At the beginning of the stimulus exposure period, differences in SBP reaction were found between aversive and neutral pictures only in the prehypertensive group (all Ps < 0.05). In contrast, during the middle of the stimulus exposure period, there was a different SBP reaction to aversive and neutral pictures only in the normotensive group (all Ps < 0.05), who reacted with a larger SBP decrease to negative compared with neutral pictures. During the recovery period, both groups showed lower levels of BP in response to aversive pictures.

In addition, similar to the DBP analysis, gender had no effect on the findings.

Finally, the covariation between SBP and DBP with HR was tested. The model examining the second-to-second covariation between HR and DBP revealed a positive relation between them ($B = 0.09$, $F(1,671) = 32.08$, $P < 0.0001$, $\Delta BIC = -18$). In addition, a positive relationship was found between HR and SBP ($B = 0.07$, $F(1,671) = 24.83$, $P < 0.0001$, $\Delta BIC = -11$). Importantly, the pattern of the findings did not change after adding HR as a predictor to the model.

Experiment 2: isometric handgrip exercise

As shown in Table 2, participants did not differ in age, BMI, anxiety and depression (all Ps > 0.05). Mean SBP and DBP measures taken before the beginning of the experiment differed between groups.

DBP reactivity

The multilevel B-spline model revealed a two-way interaction between group and time ($F(12,330) = 60.05$, $P < 0.0001$, $\Delta BIC = -30.21$). Further analyses to explain this two-way interaction focused on the differences between groups at every second during the block (see Fig. 4). The DBP reaction differed significantly between the groups during major parts of the experiment, indicating a greater BP increase in the prehypertensive group (see supplementary materials for details, http://links.lww.com/HJH/B653).

In addition, a model controlling gender resulted in similar effects. Therefore, gender did not affect the results or their pattern.

TABLE 1. Group differences for experiment 1 in demographic criteria, anxiety, depression and BP values at rest

	Group	Age	BMI	STAI- S	STAI-T	BDI	SBP	DBP
Mean (SD)	NT ($n = 25$, 10 women)	25.76 (3.66)	22.59 (2.90)	38.48 (10.36)	37.24 (7.92)	4.68 (4.67)	106.86 (8.03)	66.64 (6.78)
	PHT ($n = 25$, 8 women)	25.96 (3.20)	24.27 (4.08)	35.56 (7.80)	36.88 (7.30)	6.44 (5.44)	126.08 (4.75)	79.22 (12.03)
P value	NT	0.83	0.10	0.26	0.86	.22	0.00*	0.00*
	PHT							

Differences between groups' age, BMI, anxiety, depression, SBP and DBP taken before the beginning of the experiment. Resting SBP and DBP was greater in prehypertensive compared with normotensive participants. No other initial differences between the groups were found.
*$P < 0.001$. BDI, Beck Depression Inventory II; BP, blood pressure; STAI-S, State Anxiety Inventory; STAI-T, Trait Anxiety Inventory.

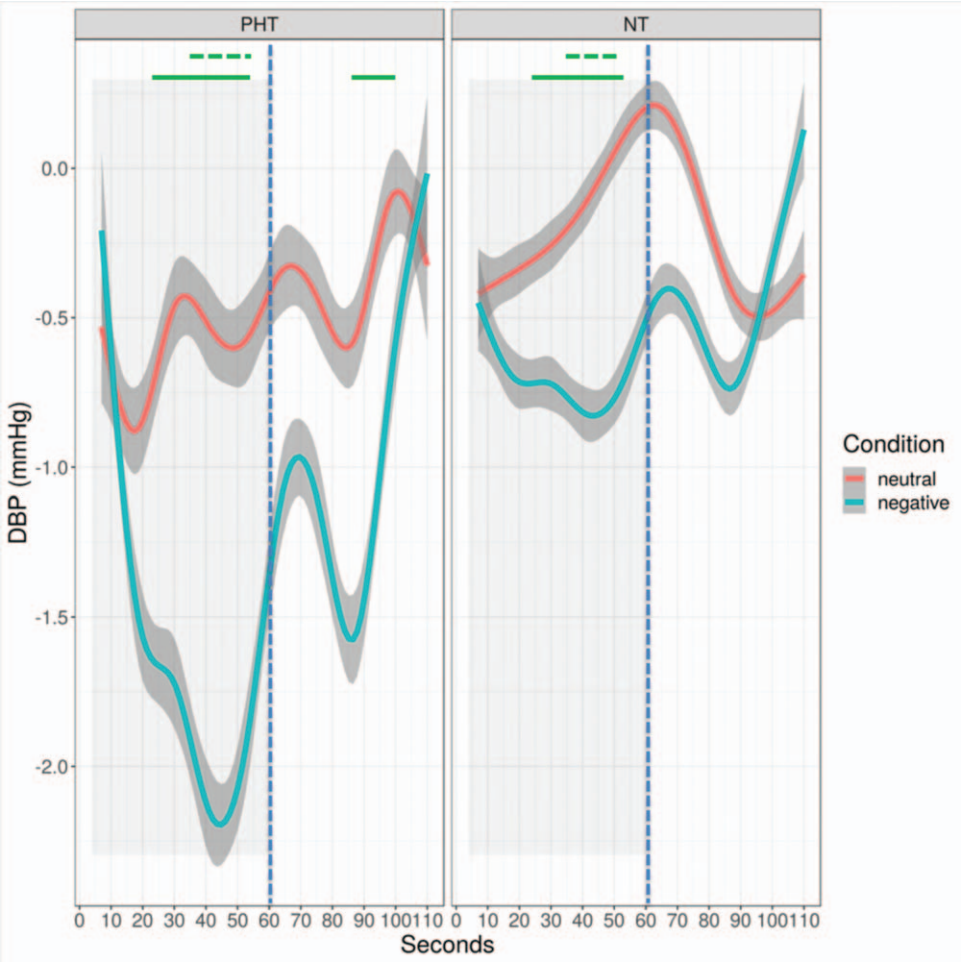

FIGURE 2 Model visualizing DBP time-course reaction in experiment 1. The DBP response of prehypertensive (PHT; $n = 25$) and normotensive (NT; $n = 25$) participants to neutral and aversive pictures. Prehypertensive individuals exhibited a decrease in DBP in response to aversive stimuli, compared with normotensive controls. In addition, slower recovery back to baseline in response to aversive compared with neutral pictures was found only in the prehypertensive group. Red lines represent the reaction to neutral pictures and blue lines represent the reaction to aversive pictures averaged across blocks during the stimulus exposure (6–60 s; the first 5 s were excluded from analysis, see text for details) and the recovery periods (60–110 s). The solid green line represents time points with significant differences in valence between groups and the dotted green line represents time points with significant differences between groups at each condition. Dotted blue lines mark the end of the stimulus exposure period (after 60 s). The gray areas are 95% confidence intervals. The baseline value – defined as the average BP during the 5 s before the beginning of each block – was subtracted from the BP values during the stimulation and recovery periods. Note that the first BP response measured during the block is not necessarily equal to the average BP in the 5 s before the block onset.

SBP reactivity

The multilevel B-spline model did not reveal a two-way interaction between group (neutral/negative) and time ($F(6,336) = 23.37$, $P < 0.0001$, $\Delta BIC = 20$). Please note that as the inclusion of the interaction between group and time did not improve the model, we conclude that there was no meaningful relation between group and time in the SBP reaction to the IHE, even though the interaction P value was below 0.05 (see Method section for more details).

In addition, controlling for gender did not change any of the effects or their pattern.

Finally, the covariation between SBP and DBP with HR was tested. The model examining the second-to-second covariation between HR and DBP revealed a positive relation between them ($B = 0.08$, $F(1,329) = 27.62$, $P < 0.0001$, $\Delta BIC = -14$). In addition, a positive relationship was found between HR and SBP ($B = 0.05$, $F(1,329) = 18.17$, $P < 0.0001$, $\Delta BIC = -7$). Importantly, the pattern of the findings did not change after adding HR as a predictor to the model.

DISCUSSION

In this study, we employed state-of-the-art measurement and analysis of continuous peripheral DBP and SBP in two different tasks, motor and emotional, to compare participants with prehypertension, a major risk factor for essential hypertension, and normotensive controls. The nonlinear model enabled dynamic observation of the BP response as well as examination of the time points throughout the experiments and revealed subtle differences between populations. The main findings of this study are that in both tasks, participants with prehypertension showed enhanced DBP reactions that significantly differed from those of the normotensive controls; and continuous analysis enabled us to better understand the time course of BP reactions to

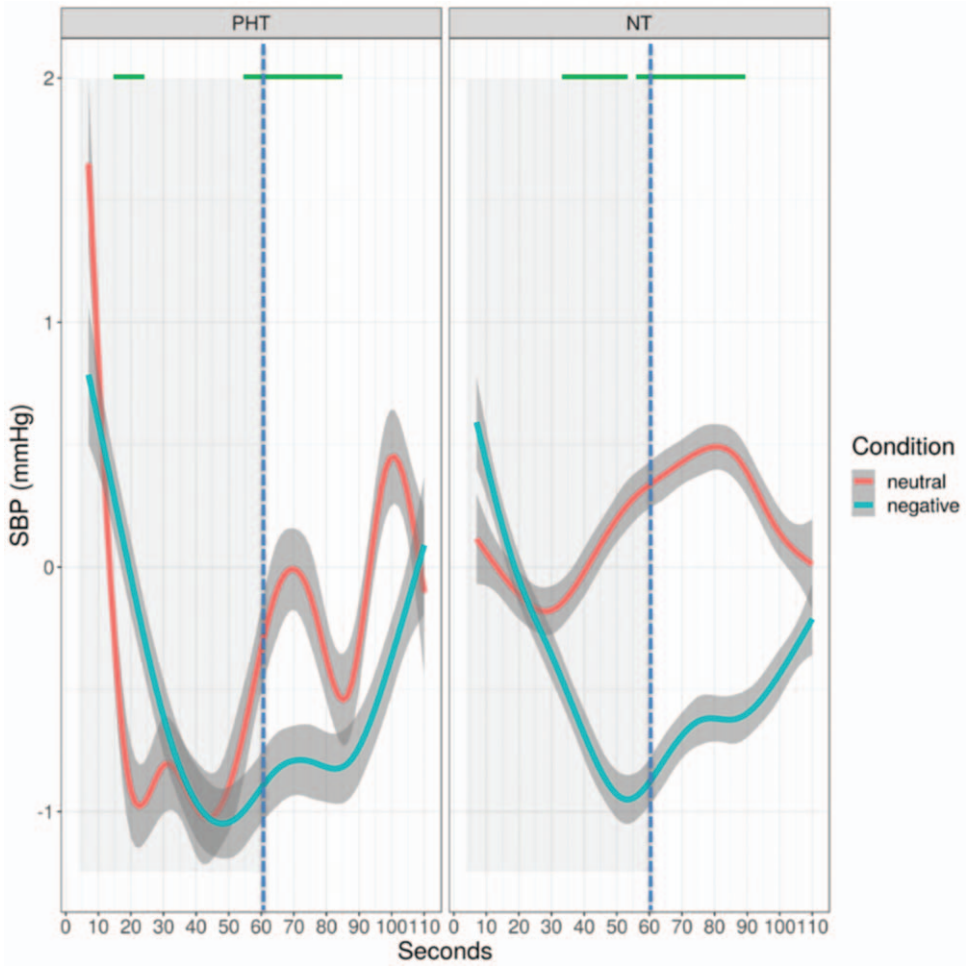

FIGURE 3 Model visualizing SBP time-course reaction in experiment 1. The SBP response of prehypertensive (PHT; $n = 25$) and normotensive (NT; $n = 25$) participants to neutral and aversive pictures. SBP reactions differed significantly between groups and valence during large parts of the stimulus exposure and recovery periods. Red represents the reaction to neutral pictures and blue represents the reaction to aversive pictures, averaged across blocks during the stimulus exposure (6–60 s; the first 5 s were excluded from the analysis, see text for details) and the recovery periods (60–110 s). The green line represents time points with significant differences in valence between groups. Dotted blue lines mark the end of the stimulus exposure period (after 60 s). The gray areas are 95% confidence intervals.

motor and emotional tasks, revealing subtle differences between prehypertensive and control participants that could not be detected using traditional analysis strategies. These results are in line with previous work who found increased BP response among patients with essential hypertension and those at risk of developing essential hypertension, compared with healthy normotensive individuals [18–22,25]. Therefore, our data extend existing findings to prehypertension and highlight the importance of continuous measurement and analysis in groups at high risk that manifest significant – albeit subtle – abnormalities in BP reactivity.

As expected, examination of the DBP response to aversive pictures showed a decline in BP levels for both groups, thought to represent enhanced attention without a need for immediate motor reaction [46,47]. These results replicate previous findings with healthy participants as well as with participants with essential hypertension [26–30]. A similar decline in autonomic reaction following aversive pictures has also been demonstrated in HR [48,49]. Although both groups showed a decrease in DBP, prehypertensive participants exhibited a larger and steeper decrease following exposure to aversive compared with neutral pictures. Gupta [50] suggested that the decline in BP levels is because

TABLE 2. Group differences for experiment 2 in demographic criteria, anxiety, depression and blood pressure values at rest

	Group	Age	BMI	STAI- S	STAI-T	BDI	SBP	DBP
Mean (SD)	NT ($n = 28$, 5 females)	26.55 (4.01)	3.2 (3.21)	36.16 (9.82)	35.56 (8.13)	3.2 (3.71)	111.92 (9.69)	65.94 (4.50)
	PHT ($n = 29$, 7 females)	26.64 (3.77)	6.15 (3.24)	36.66 (7.82)	36.48 (7.82)	6.15 (5.42)	129.70 (6.73)	75.96 (6.51)
P value	NT	0.93	0.035*	0.829	0.664	0.01*	0.000*	0.000*
	PHT							

Differences between groups' age, BMI, anxiety, depression, SBP and DBP taken before the beginning of the experiment. BMI, BDI and resting SBP and DBP were greater in prehypertensive compared with normotensive participants. No other initial differences between the groups were found. BDI, Beck Depression Inventory II; BP, blood pressure; STAI-S, State Anxiety Inventory; STAI-T, Trait Anxiety Inventory.

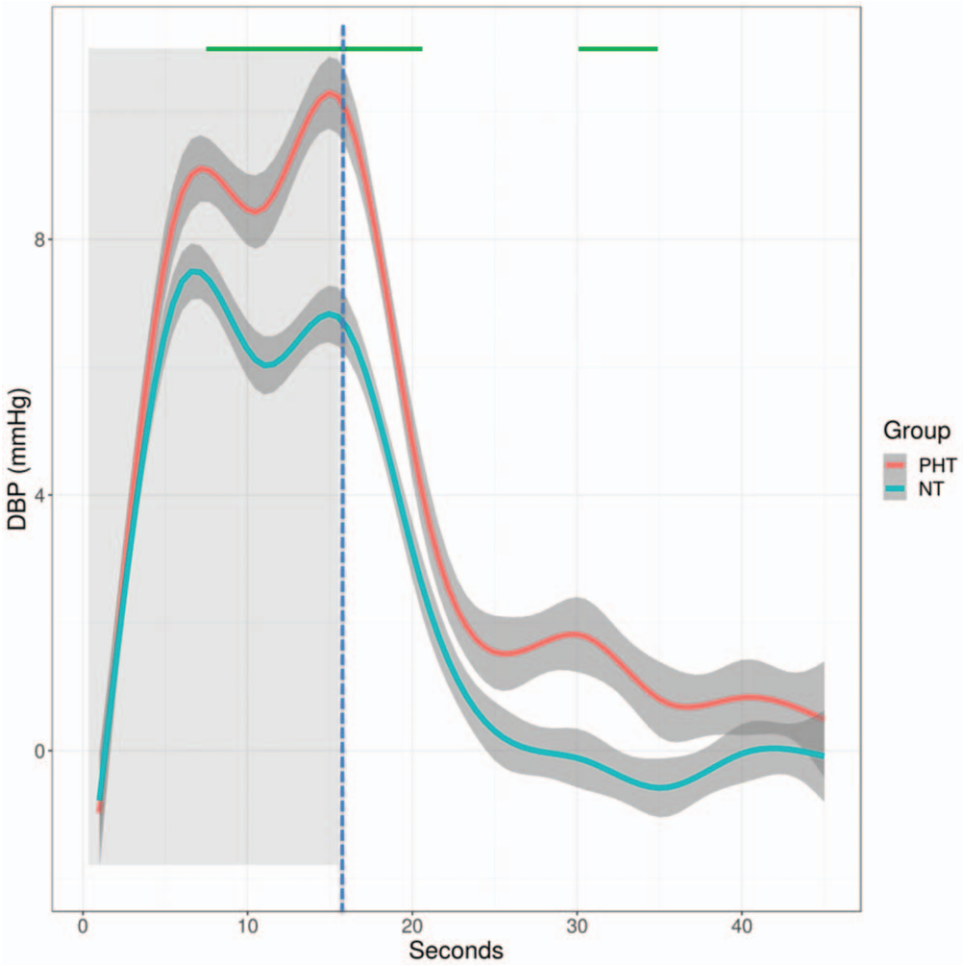

FIGURE 4 Model visualizing DBP time-course reaction in experiment 2. Comparison of the DBP response to the IHE between prehypertensive (PHT; represented in blue; $n = 29$) and normotensive (NT; represented in red; $n = 28$) participants. Prehypertensive individuals exhibited a higher DBP increase compared with normotensive controls. BP reaction is averaged across blocks during the exercise (0–15.5 s) and the resting periods (15.5–45.5 s). The green line represents time points with significant differences between groups. Dotted blue lines mark the end of the exercise period (after 15.5 s). The gray areas are 95% confidence intervals.

of activation of feedback mechanisms in brain regions associated with emotional processing. The greater decline in DBP observed in prehypertensive participants in response to emotional stimuli may indicate abnormalities in neurocognitive emotional processing mechanisms. The decline in DBP during the stimulation block was followed by a slower return to baseline during recovery from aversive stimulation in the prehypertensive group. These findings are in line with Erdogan *et al.* [51] who showed slower HR return to baseline in response to physical exercise among prehypertensive participants, and argued that the autonomic dysregulation that characterizes essential hypertension is already present at the prehypertensive stage. Results of SBP responses are more difficult to interpret. The normotensive group showed larger and more substantial differences between aversive and neutral pictures, compared with the prehypertensive group. The prehypertension group, however, appeared to show greater reactions to both aversive and neutral pictures, compared with the normotensives.

These findings indicate that prehypertensive participants have enhanced reactivity not only to mental stress, as previously shown [21–23] but also to emotional situations that characterize everyday life. Such enhanced emotional reaction may be because of dysfunctional neurocognitive inhibitory mechanisms related to emotion regulation in prehypertension. Indeed, there is evidence for abnormalities in prefrontal–limbic neural pathways among patients with essential hypertension and those at high risk [21–23]. In addition, there is evidence for higher levels of anxiety and depression in essential hypertension or prehypertension [52–54] (although observations are inconsistent [55,56]). Taken together, these different lines of evidence suggest deficits in inhibitory emotion control in prehypertension. Recently, we [57] hypothesized that dysfunctional inhibitory prefrontal–parietal mechanisms in essential hypertension lead to enhanced activation in limbic areas that include the amygdala, insula and cingulate cortex, which in turn lead to elevated levels of anxiety and depression, as well as abnormalities in brainstem and baroreflex systems that result in enhanced BP reactions in essential hypertension. The current findings suggest that such dysfunctional mechanisms may exist already at the prehypertensive stage.

Our findings of elevated SBP and DBP were demonstrated during IHE in both groups. Yet, higher and steeper

DBP levels were found in the prehypertensive participants compared with the normotensive group. This increase is in line with previous studies that found greater elevation in mean arterial BP and enhanced metaboreflex sensitivity and sympathetic responses in participants with essential hypertension and those at risk of developing essential hypertension compared with normotensive controls [14–16,19,58,59]. Previous studies demonstrated that the isometric hand grip increases BP through release of plasma norepinephrine and epinephrine and increased peripheral resistance (vasoconstriction). Cardiac output does not increase, or even mildly decreases, during the task [59] because of a decrease in stroke volume and an increase in HR. The exaggerated BP response in patients with essential hypertension may theoretically be attributed to increased signal (norepinephrine and epinephrine) or increased response to the signal (vasoconstriction). Gonzalez *et al.* [59], however, showed similar norepinephrine and epinephrine responses during IHE in hypertensive patients compared with normotensives, and thus the difference may be attributed to exaggerated vasoconstriction in response to similar norepinephrine and epinephrine release.

The fact that enhanced reactions were found across two different tasks suggests abnormality in shared underlying physiological mechanisms, which are not specifically related to emotional or motor reactions. Such mechanisms may be the baroreceptive system, known to have a major role in BP regulation [33] or an autonomic dysregulation [51,60,61]. An alternative explanation is that these two tasks activate different autonomic mechanisms – one emotional [21,22,50,62] and the other, motor [58,59], both of which are impaired in prehypertensive participants. In both experiments, differences between groups were found mainly in DBP. DBP serves as a stronger predictor of cardiovascular diseases compared with SBP for individuals under the age of 50 years [63,64].

In both experiments, the pattern of the findings did not change after adding HR as a predictor to the model. These findings demonstrate that HR cannot explain the differences between prehypertensive participants and normotensives in BP reactions and suggest these differences are because of systems that are specific to BP reactivity. Similarly, the group differences cannot be explained by abnormality in heart functioning. Future studies should examine additional peripheral measures, such as stroke volume or arteries' blockage, as well as neural activation, in order to understand the specific mechanisms that lead to abnormal reactivity in prehypertension.

Due to the changes in BP guideline classifications, prehypertension values now refer to 'Elevated' and 'Stage 1 hypertension' according to American Heart Association [65] and 'Normal' and 'High normal' according to the European guidelines [66]. Our results, indicating abnormalities in the prehypertensive stage, support the 'American Heart Association' new classification by indicating that prehypertension is a group that should already be treated.

The continuous measurement and analysis employed in the current study allowed us to characterize the time course of BP reactivity in prehypertension. This approach highlighted differences not only in an averaged or maximum reaction values but in the time course of responses. Specifically, the continuous analysis strategy demonstrated steeper reactivity in prehypertension in both tasks, which could not have been detected in standard linear analysis. A better understanding of the timecourse of BP reaction in prehypertensive participants compared with normotensives may assist in developing more fine-tuned diagnostic protocols for early detection of abnormal BP reactivity, which in turn may result in prevention of hypertension.

To the best of our knowledge, this study is the first to compare the continuous BP reaction to mild aversive stimulation and IHE among prehypertensive participants, allowing for a deeper understanding of the BP response among this risk group. Nevertheless, it is not free of limitations. One limitation is that other than BP, we did not measure any other physiological indices, such as epinephrine, norepinephrine, brain activity, baroreceptors function, stroke volume or HR variability. Therefore, our physiological understanding and explanations should be further examined directly in future studies. In addition, as noted, exclusion criteria included history of substance abuse, neurologic diseases, psychiatric disorders, cardiovascular diseases or any other chronic diseases. Participants were also instructed to refrain from consuming caffeine and from engaging in physical exercise and smoking 3 h prior to participating in the experiment. Nevertheless, we did not measure blood biochemistry, and therefore, cannot completely rule out acute or chronic conditions, such as renal failure or electrolyte abnormality that the participants were not aware of.

In conclusion, considering the high frequency and health risks related to prehypertension [1,7,8], understanding the autonomic reactions to emotional and motor stimuli in this population is of crucial clinical and theoretical importance. We demonstrate abnormally enhanced emotional and motor responses in prehypertension, suggesting abnormalities already exist in the prehypertensive stage. Such abnormal, enhanced reactions can potentially serve as a behavioural marker for identification of at-risk groups.

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Conflicts of interest

There are no conflicts of interest.

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