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Nociceptive flexion reflex thresholds and pain during rest and computer game play in patients with hypertension and individuals at risk for hypertension

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Abstract

Supraspinal pain modulation may explain hypertensive hypoalgesia. We compared nociceptive flexion reflex (NFR) thresholds and pain during rest and computer game play in hypertensives and normotensives (Experiment 1) and normotensives with and without hypertensive parents (Experiment 2). The game was selected to modulate activity in pain pathways. NFR thresholds did not differ between groups during rest or game play. Pain ratings never differed between hypertensives and normotensives, whereas individuals with hypertensive parents reported less pain during the first two NFR assessments, compared to those without. NFR thresholds and pain were reduced by game play compared to rest. The failure of game play to differentially modulate NFR thresholds or associated pain reports between groups argues against enhanced supraspinal modulation of nociception and pain in hypertensives and those at increased risk for hypertension.

Keywords

Hypertension; Nociceptive flexion reflex threshold; Pain; Risk for hypertension; Supraspinal pain modulation

1. Introduction

Since it was first reported that high blood pressure in humans is characterised by reduced sensitivity to pain (Zamir and Shuber, 1980), evidence has accumulated from 25 years of research to establish the phenomenon of hypertensive hypoalgesia (for review see Ghione, 1996). Numerous studies have documented that, compared with normotensive individuals, those with hypertension are characterised by reduced pain in response to noxious stimulation.

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Hypoalgesia has also been found in borderline hypertensives compared to normotensives (Elbert et al., 1988; Rau et al., 1994; Rosa et al., 1986; Schobel et al., 1996, 1998). Moreover, hypoalgesia can extend into the normotensive blood pressure range in young adults at increased risk for hypertension, such as those with a parental history of hypertension, elevated resting blood pressure, or exaggerated cardiovascular reactivity to stress (Campbell and Ditto, 2002; France, 1999), although there are exceptions (al'Absi et al., 2000; Ghione et al., 1988).

Studies have demonstrated hypertensive hypoalgesia using noxious electrical tooth pulp, thermal, mechanical and electrocutaneous stimulation and have relied on participants' subjective responses to assess pain. An alternative approach is to obtain a measure of nociception, while also collecting the associated pain ratings, using the nociceptive flexion reflex (NFR), a polysynaptic spinal reflex that facilitates withdrawal from noxious stimuli to avoid tissue injury (Sherrington, 1906). It is worth noting the important distinction between pain and nociception. Nociception is the neural transmission of information about a potential or actual tissue damaging stimulus. Noxious insult to the skin causes activation of peripheral nociceptors which excite nociresponsive neurons in the spinal cord dorsal horn. Activity in these dorsal horn neurons relays nociceptive information to higher brain centres to be processed. Pain can be defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage and, importantly, it is not a direct product of activity of nociceptive afferent fibres. The NFR threshold provides a naturally-occurring, objective physiological correlate of nociception (for review see Sandrini et al., 2005). In the NFR paradigm, a withdrawal response can be elicited in the short head of the ipsilateral biceps femoris muscle in the lower limb by electrocutaneous stimulation of the sural nerve in the retromalleolar path at an intensity sufficient to activate A-delta nociceptive fibres (Dowman, 1991; Kugelberg et al., 1969; Wiesenfeld-Hallin et al., 1984; Willer, 1983). The electromyographic response in the biceps femoris can be used to quantify nociceptive responding or help determine the threshold for eliciting a withdrawal response. There is evidence that increased levels of sural nerve stimulation are associated with increased pain ratings and NFR responses (Sandrini et al., 2005).

The NFR paradigm has never been used to assess nociception in individuals with hypertension. However, a number of studies have employed the NFR to investigate the influence of risk for hypertension on nociception (France et al., 2002; France and Suchowiecki, 2001; Page and France, 1997). These studies of normotensive undergraduates (France et al., 2002; France and Suchowiecki, 2001; Page and France, 1997) have shown that NFR thresholds are higher in individuals with a positive parental history of hypertension compared to those with a negative parental history. Thus, the current study set out to investigate the influence of hypertension and risk for hypertension on nociceptive responding compared to normotensives. It was anticipated that hypertensives would have higher NFR thresholds, indicative of reduced nociceptive responding, compared to normotensive controls during rest. Further, in line with previous studies demonstrating increased NFR thresholds in those normotensives at risk for hypertension, it was expected that those at risk for hypertension, based on either their mother or father being hypertensive, would show higher NFR thresholds compared to controls.

1.1. Supraspinal Modulation of Pain—The pain experience can be affected by psychological processes. Research demonstrates that pain can be modulated centrally by variations in attention (Miron et al., 1989; Tracey et al., 2002; Villemure and Bushell, 2002; Weisenberg, 1987) and arousal (Bandler et al., 2000; Maixner, 1991). Both distraction from noxious stimulation and increased arousal (Maixner, 1991) have been associated with reductions in pain (Miron et al., 1989; Weisenberg, 1987).

Nociceptive transmission at the spinal cord dorsal horn is tonically modulated by the descending influence of the midbrain periaqueductal gray (Behbehani, 1995; Wall and

Melzack, 1999). Such antinociception is thought to result in inhibition of nociceptive neurons in the dorsal horn (Liebeskind et al., 1973), directly and via the nucleus raphe magnus of the rostral ventromedial medulla (Gebhart et al., 1983). Thus, the periaqueductal gray modulates the amount of nociceptive information which is transmitted to higher brain centres, and hence, affects the magnitude of pain experienced. In this way, the pain experience does not necessarily reflect the intensity of the peripheral noxious stimulus that evokes it. Neuroanatomical evidence suggests that distraction may influence pain by modulating activity within the periaqueductal gray. The periaqueductal gray receives afferents from forebrain limbic areas, including the prefrontal cortex (An et al., 1998; Bandler and Shipley, 1994; Hardy and Leichnetz, 1981; Keay and Bandler, 2001), amygdala (Gray and Magnuson, 1992; Paredes et al., 2000; Rizvi et al., 1991) and hypothalamus (Behbehani et al., 1988; Reichling and Basbaum, 1991). Stimulation of these limbic areas, known to be activated by attention, stress and sympathoexcitation, increases activity in the periaqueductal gray (Behbehani et al., 1988; Hardy and Haigler, 1985) and inhibits dorsal horn nociceptive neurons (Carstens et al., 1983). Further, neuroimaging studies confirm that distracting pain-attenuating conditions activate central nervous system structures involved in pain modulation, such as the periaqueductal gray (Petrovic et al., 2000; Tracey et al., 2002). Accordingly, it is possible that individuals with hypertension or at increased risk for the disorder experience less pain due to differential activation of these pain inhibition pathways (see France and Ditto, 1996; France, 1999).

1.2. Supraspinal Modulation of the Nociceptive Flexion Reflex—Considerable anatomical and empirical evidence suggests that the NFR is subject to tonic inhibition from several supraspinal structures involved in pain modulation (Dimitrijevic and Nathan, 1968; Sandrini et al., 1993; Willer, 1983). For example, NFR responses are exaggerated in spinal patients compared to intact individuals (see Sandrini et al., 2005). Accordingly, it has been suggested that the NFR threshold may index descending central nervous system influence on spinal nociceptive transmission. Indeed, changes in psychological state modulate the NFR. For example, early research by Bathien suggested that NFR responding was reduced by secondary tasks designed to direct attention away from the electrocutaneous stimulation, such as figure tracing and number addition tasks (Bathien, 1971; Bathien and Hugelin, 1969; Bathien and Morin, 1972). That these distraction tasks, chosen for their minimal motor demands, increased participants' heart rates and ventilation rates, indicates that they were also arousing. Thus, it is difficult to attribute such NFR attenuation to distraction per se. Willer et al. (1979) have also reported that mental arithmetic attenuated the NFR response. In contrast, other studies have shown that NFR responses were facilitated by a selective attention task (Bathien and Morin, 1972) whilst mental arithmetic reduced NFR thresholds (Edwards et al., 2006; Petersen et al., 2001) and facilitated nociceptive responding (McIntyre et al., 2006) compared to rest. Recent studies have also found that NFR thresholds (France et al., 2002) and NFR responding (Terkelsen et al., 2004) were uninfluenced by mental arithmetic tasks, while pain was reduced. In sum, although early studies suggested that directing attention away from the noxious stimulus attenuates the NFR, this evidence is contradicted by more recent findings. The inconsistencies in this literature may reflect variations in the levels of distraction and arousal associated with the secondary tasks, which in turn reflect the extent to which the tasks engage supraspinal pain modulatory systems.

The current study aimed to examine the function of the supraspinal pain modulatory system in hypertension and risk for hypertension. Thus, NFR thresholds were assessed while participants rested and while they played the computer game Tetris®. This computer game involves visual-spatial and motor functions similar to a perceptual maze task used in neuroimaging research concerning the effects of distraction on pain (Petrovic et al., 2000; see also Ghatan et al., 1995). In addition, preliminary research in young normotensive undergraduates has demonstrated that playing Tetris caused a reduction in pain ratings and NFR thresholds. Playing

this computer game has also been found to be more distracting and to cause faster heart rates and greater cardiac contractility, indexes of physiological arousal, compared to rest (Edwards et al., 2003b). Tetris was also judged to be similarly distracting and arousing as mental arithmetic compared to rest (Edwards et al., 2003b). Mental arithmetic has been shown to reduce NFR thresholds and increase nociceptive responding compared to rest (Edwards et al., 2006;McIntyre et al., 2006). Based on these previous studies, computer game play was chosen as a method of activating central nervous system pathways involved in pain modulation. In keeping with our previous studies that assessed the NFR during both Tetris and mental arithmetic (Edwards et al., 2003b;Edwards et al., 2006;McIntyre et al., 2006); it was expected that a distracting and arousing secondary task, Tetris, would cause a reduction in NFR thresholds, indicative of enhanced nociceptive activity in the spinal cord. The mechanism by which arousing and distracting cognitive tasks, such as Tetris, could augment activity in nociceptive spinal neurons is unclear, however, it may be caused by either withdrawal of midbrain periaqueductal gray inhibition or increased facilitatory influence from heightened activity in either the reticular activating system or on-cells in the rostral ventromedial medulla (Wall and Melzack, 1999). Based on the findings of previous studies (Edwards et al, 2003b; 2006;McIntyre et al., 2006), it was also predicted that pain would be reduced during Tetris compared to rest. This prediction fits with the well established literature showing that distraction from noxious stimulation (Miron et al., 1989;Weisenberg, 1987) and increased arousal (Maixner, 1991) are associated with a reduction in pain. As these previous studies have reported that the NFR is enhanced while pain is attenuated during Tetris, this implies that the reduction in pain sensation could not be due to inhibition of spinal nociceptive input and is more likely due to pain suppression at higher brain centres. If hypertension is characterised by abnormal function of the supraspinal pain modulatory system, it might be expected that playing Tetris would cause a differential modulation of the NFR compared to normotensives. For example, normotensives might be expected to show a reduction in NFR thresholds during computer game play, compared to rest, indicating a reduction in tonic supraspinal modulation of nociception by computer game play. In contrast, hypertensives might be expected to show higher NFR thresholds than normotensives during rest, indicative of enhanced supraspinal inhibition, and no reduction in NFR thresholds during Tetris, indicating an already fully engaged supraspinal pain modulatory system. However, if hypertensives were to demonstrate a similar pattern of modulation to normotensives, then this would suggest that hypertension is associated with a normal pain modulatory system.

Thus, the current study examined the effects of performing a secondary cognitive task – the computer game Tetris® – on NFR thresholds in two concurrent studies; one in the United Kingdom and one in the United States. In Experiment 1, NFR thresholds were determined in middle-aged patients with hypertension and in normotensive individuals. In Experiment 2, NFR thresholds were determined, using an identical methodological design, in young normotensive adults with and without a parental history of hypertension. In both cases, it was expected that nociceptive thresholds would be influenced by hypertension status, both at rest and during the computer game task. As previous studies investigating hypertensive hypoalgesia have used subjective pain ratings, the current study also obtained a measure of multidimensional pain using the short form McGill pain questionnaire (Melzack, 1987), which was completed by participants after each NFR threshold determination.

Experiment 1

2. Method

2.1. Participants—Seventy adults were recruited but complete NFR thresholds could not be determined for seven participants. Thus, the effective sample comprised 35 newly-diagnosed and unmedicated essential hypertensive adults and 28 normotensive controls. Their characteristics are summarized in Table 1. Patients were recruited from the Hypertension Clinic

at University Hospital Birmingham, UK, and were tested before they had started pharmacological treatment for hypertension. Normotensive volunteers were recruited from the general population of Birmingham, UK. All participants were screened in the clinic. The study was approved by the local ethics committee and volunteers gave written consent prior to participation.

2.2. Screening

Exclusion criteria In an initial screening session, each participant's medical status and eligibility were determined. The following exclusion criteria were applied: current use of prescription medication, diabetes mellitus, cerebrovascular disease, angina, myocardial infarction, peripheral vascular disease, neurological disease, chronic liver disease, high alcohol intake (greater than 21 units/week of alcohol for women and 28 units/week for men), major psychiatric disorder, and secondary hypertension including chronic renal failure, renal artery stenosis, Conn's syndrome, or pheochromocytoma.

Blood pressure status British Hypertension Society guidelines (Ramsay et al., 1999) were used to establish blood pressure status. Each participant's blood pressure was measured for 24 hours using an ambulatory blood pressure monitor (SpaceLabs Medical, Madison, USA, Model 90207). Patients with systolic blood pressure (SBP) ≥ 160 mmHg or diastolic blood pressure (DBP) ≥ 100 mmHg at referral, and confirmed at clinic and by mean daytime ambulatory pressure were diagnosed as hypertensive; 94% of patients met these classification criteria. Patients with a SBP of 140–159 mmHg and/or DBP of 90–99 mmHg at referral, clinic, and ambulatory measurements were also diagnosed as hypertensive if their 10 year coronary heart disease risk was $\geq 15\%$ and/or there was evidence of left ventricular hypertrophy on a 12 lead electrocardiograph or echocardiograph, or there was other evidence of end organ damage. The cardiovascular risk profile was calculated using the Joint British Societies Cardiac Risk Assessor computer program (Wood et al., 1998). Blood was sampled to determine renal function, potassium, glucose, cholesterol, high-density lipoprotein, and triglycerides. Urinalysis was also performed. If clinically indicated, patients were screened for evidence of secondary hypertension with renal ultrasound and 24 hour urinary collection for catecholamine, renin and aldosterone levels. Participants were classified as being normotensive if they had SBP < 140 mmHg and DBP < 90 mmHg, confirmed on ambulatory blood pressure monitoring, and $< 15\%$ risk of coronary heart disease in the next 10 years.

2.3. Physiological Measurements—Participants sat upright in a comfortable chair with their left ankle supported so the knee was flexed at 35° . A computer and Micro1401 (CED) were programmed in Spike2 (CED) to present stimuli and record responses. SBP (mmHg), DBP (mmHg), and heart rate (HR, bpm) were obtained using an oscillometric sphygmomanometer (Dinamap, Critikon) and a brachial cuff attached to the participant's upper left arm. Electromyographic activity of the left biceps femoris muscle was recorded at 2000 Hz using a Bagnoli-2 amplifier (20–450 Hz, $\times 10000$) and single differential surface electrode (Delsys) with a separate reference electrode (for further details see Edwards et al., 2003a). The sural nerve was stimulated using a constant current stimulator (DS7A, Digitimer) and bar electrode (Nicolet) that was secured posterior to the ankle. Sites were prepared using alcohol-swabs and abrasive gel until electrode impedance was $< 10 \Omega$. Conductive cream was applied to electrode contacts.

2.4. Procedure—Participants completed two three-hour morning sessions that were counterbalanced across participants. They were instructed to refrain from caffeine, alcohol, and vigorous exercise for 2 hours, and analgesic medication for 24 hours prior to testing. They were paid £30 for participating. At the start of the session, participants sat and relaxed during an initial formal rest period (10 min) while their blood pressure was measured four times. The

investigator then administered a tablet to the participant, which contained either a 50 mg dose of naltrexone or placebo (only the data from the placebo session are presented here; the effects of opioid blockade on pain tolerance are reported elsewhere by Ring et al (under review)). The participant sat quietly for 1 hour. During this rest period the sites were prepared and electrodes attached for measuring the NFR. They then completed a second formal rest period (10 min) while their blood pressure was measured four times. Three NFR threshold assessments were then performed (30–60 min) with a 5 min recovery period after each assessment.

2.4.1. Nociceptive Flexion Reflex Threshold Assessment The NFR threshold was determined using an adaptive up-down staircase procedure. The sural nerve was stimulated by five 1-ms rectangular-wave pulses at 250 Hz, 200 ms into each 1 s trial. The NFR was operationally defined as a mean rectified electromyographic response in the 90–150 ms post-stimulus interval that exceeded mean rectified electromyographic activity during a 60 ms pre-stimulus baseline interval (–65 to –5 ms) by at least 1.5 *SD*. Stimulus intensity increased in 4 mA steps, starting at 0 mA, until the NFR was first detected, and then decreased in 2 mA steps until the nociceptive flexion reflex was not detected. The staircase continued in 1 mA steps for four more reversals, which were averaged to yield the NFR threshold (mA). A variable (15, 20, 25 s) inter-trial interval was used. Maximum stimulation intensity was 40 mA. The NFR threshold was determined during three consecutive conditions: while sitting quietly (first rest), while playing the computer game Tetris (task), and while sitting quietly (second rest). Each assessment lasted approximately 5 minutes. Participants practiced playing the computer game at the start of the session. Computer game play was timed to commence with the initiation of NFR assessment and continued until the NFR threshold was determined. The computer game required the participant to press buttons on a hand-held console to rotate and move a series of falling oddly-shaped blocks to fit optimally into spaces at the bottom of the screen. Computer game performance was not recorded. Individuals who were good at the task progressed to higher more difficult levels of the game, whereas those who were poor repeated playing the easy levels of the game. Accordingly, task difficulty was effectively matched to individual differences in spatial abilities. Participants completed Melzack's (1987) short-form McGill Pain Questionnaire immediately after each threshold determination to indicate retrospectively the overall pain associated with the electrocutaneous stimulations delivered during the threshold procedure, which took approximately 2 minutes. Participants rated 11 sensory and four affective descriptors on an intensity scale of 0 (none), 1 (mild), 2 (moderate), and 3 (severe) that were summed to yield the total pain rating index. A scale, with anchors of 0 (no pain) and 100 (worst possible pain), was used to indicate an overall pain rating.

2.5. Data Reduction and Analysis—The set of four resting blood pressure and pulse recordings, taken after resting for 1 hour, were averaged to provide measures of resting laboratory SBP, DBP, and HR. Analyses were largely by Group by Sex by Condition repeated measures analyses of covariance (MANCOVA), with Group and Sex as between-subjects factors, and Condition as a within-subjects factor; the assumptions of homogeneity of variance and homogeneity of regression were met. Preliminary analyses performed with Session as a between-subjects factor revealed no session effects, and therefore, in the analyses reported below, session was not included as a factor. Eta-squared (η^2), a measure of effect size, is reported. Differences in the reported degrees of freedom reflect occasional missing data.

3. Results

3.1. Blood Pressures and Demographics—A series of 2 Group (hypertensive, normotensive) analyses of variance (ANOVAs) confirmed that the hypertensive patients had significantly higher ambulatory SBP, $F(1, 55) = 77.64, p = .000001, \eta^2 = .585$, ambulatory DBP, $F(1, 55) = 46.63, p = .000001, \eta^2 = .459$, laboratory SBP, $F(1, 61) = 45.29, p = .000001, \eta^2 = .426$, and laboratory DBP, $F(1, 61) = 32.23, p = .000001, \eta^2 = .346$, compared to the

normotensive controls. Laboratory heart rates did not differ between groups, $F(1, 61) = 2.18$, $p = .15$, $\eta^2 = .035$. The summary data are shown in Table 1. In terms of demographics, the groups did not differ in sex, $\chi^2(1) = 1.83$, $p = .18$, or body mass index, $F(1, 61) = 0.01$, $p = .96$, $\eta^2 = .001$. The hypertensive group was, however, older than the normotensive group, $F(1, 61) = 5.68$, $p = .02$, $\eta^2 = .085$, and therefore, age was entered as a fixed covariate in the subsequent analyses involving between-subjects factors.

3.2. Nociceptive Flexion Reflex Thresholds—A 2 Group (hypertensive, normotensive) $\times$ 2 Sex (male, female) $\times$ 3 Condition (first rest, task, second rest) MANCOVA, with age as a covariate, on the NFR thresholds yielded a significant condition effect, $F(2, 58) = 10.29$, $p = .0001$, $\eta^2 = .262$. Neuman Keuls post hoc comparisons confirmed that the threshold for eliciting the NFR was lower during the computer game task ($M = 13.9$, $S.D. = 9.9$ mA) than the first rest ($M = 15.6$, $S.D. = 9.8$ mA), which in turn, was lower than during the second rest ($M = 17.1$, $S.D. = 10.3$ mA). Neither the main effect for group nor the interaction effect for group and condition (see Table 2) were significant. No effects for sex emerged.

3.3. Pain Ratings—Separate 2 Group $\times$ 2 Sex $\times$ 3 Condition MANCOVAs, with NFR thresholds as the changing covariates to adjust for differences in the stimulation levels, yielded significant condition effects for the McGill Pain Questionnaire total pain rating index, $F(2, 56) = 7.69$, $p = .001$, $\eta^2 = .216$, and overall pain rating, $F(2, 55) = 8.21$, $p = .001$, $\eta^2 = .230$. Post hoc analyses revealed that participants experienced less pain during the computer game task than both the first and second rests: the means ($S.D.$) were 4.8 (3.8) versus 7.3 (4.7) and 6.7 (4.5) respectively for the total pain rating index; and 29.4 (20.0) versus 40.9 (23.6) and 41.4 (23.9) for the overall pain ratings. However, the group by condition interaction effect was not significant (see Table 2). Group $\times$ 2 Sex $\times$ 3 Condition MANCOVAs, with age as the fixed covariate to adjust for age differences between groups and sexes, yielded no significant effects for group or sex.

Experiment 2

4. Method

4.1. Participants—One-hundred and fifty-three young adults were recruited but 38 did not provide full data. Thus, the effective sample comprised 46 participants with a positive parental history of hypertension and 69 with a negative parental history of hypertension. Their characteristics are summarized in Table 3. Patients were recruited from the general population at Ohio University and the University of Minnesota, USA. All participants were screened by a doctor before participating. Female participants were scheduled so that their laboratory sessions fell within 2-7 days after the onset of menses. The study was approved by local ethics committees and volunteers gave written consent prior to participation.

4.2. Screening

Exclusion criteria In an initial screening session, each participant's health status and eligibility were determined. The following exclusion criteria were applied: current use of prescription medication (other than birth control), pregnant, and a history of major medical problems.

Parental history of hypertension A blood pressure history survey (Page and France, 2001) was mailed to the biological parents of participants to confirm parental hypertension and anti-hypertensive medication history. Participants were classified as having a positive parental history of hypertension if at least one parent indicated that they had been diagnosed with hypertension by their physician and been treated with anti-hypertensive medication. Hypertensive parents were asked to provide the name of their medication(s) as confirmation of diagnosis and treatment. In an attempt to restrict the sample to offspring of essential

hypertensives, participants were not included if their parents reported a history of diabetes or kidney disease.

4.3. Physiological Measurements, Procedure, Data Reduction and Analysis—

The measurements were the same as described in Experiment 1, except for blood pressure which was measured seven times during the course of a separate 30-min blood pressure assessment session. The procedure was the same as described in Experiment 1 except for the measurement of blood pressure. The opioid blockade results have been reported by France et al. (2005). The data reduction and analysis were similar to Experiment 1, except that the set of seven blood pressure and pulse recordings were averaged to provide measures of resting laboratory SBP, DBP, and HR.

5. Results

5.1. Blood Pressures and Demographics—A series of 2 Group (positive parental history of hypertension, negative parental history of hypertension) ANOVAs confirmed that the laboratory SBP, $F(1, 113) = 0.62, p = .80, \eta^2 = .001$, DBP, $F(1, 113) = 0.61, p = .44, \eta^2 = .001$, and HR, $F(1, 113) = 1.53, p = .22, \eta^2 = .013$, did not differ between groups. Moreover, groups did not differ in sex, $\chi^2(1) = 1.75, p = .19$, body mass index, $F(1, 113) = 2.58, p = .11, \eta^2 = .022$, or age, $F(1, 113) = 0.00, p = .98, \eta^2 = .001$. The summary data are shown in Table 3.

5.2. Nociceptive Flexion Reflex Thresholds—A 2 Group $\times$ 2 Sex $\times$ 3 Condition MANOVA on the NFR thresholds yielded a significant condition effect, $F(2, 110) = 16.64, p = .0005, \eta^2 = .232$. Neuman Keuls post hoc comparisons confirmed that the NFR threshold was lower during the computer game task ($M = 11.5$, S.D. = 7.6 mA) than the first rest ($M = 12.4$, S.D. = 7.1 mA), which in turn, was lower than during the second rest ($M = 13.6$, S.D. = 8.0 mA). Neither the main effect for group nor the interaction effect for group and condition (see Table 4) were significant. Finally, the men ($M = 13.8$, S.D. = 6.7 mA) exhibited higher thresholds than the women ($M = 11.2$, S.D. = 7.1 mA), $F(1, 111) = 3.88, p = .05, \eta^2 = .034$.

5.3. Pain Ratings—To examine the effect of performing the computer game task on pain, two 2 Group $\times$ 2 Sex $\times$ 3 Condition MANCOVAs, with NFR thresholds as changing covariates, were conducted. The first analysis, which used overall pain ratings as the dependent measure, revealed a significant condition effect, $F(2, 106) = 4.86, p = .01, \eta^2 = .086$. As can be seen in Table 4, overall pain ratings were significantly lower during the computer game task ($M = 33.1$, S.D. = 21.8) compared to the first ($M = 37.7$, S.D. = 22.1) and second ($M = 36.0$, S.D. = 22.3) rests. There were no other significant effects. The second analysis, which used total pain rating index scores from the McGill Pain Questionnaire as the dependent measure, revealed a significant condition effect, $F(2, 107) = 4.65, p = .01, \eta^2 = .080$, as well as a significant group by condition interaction, $F(2, 107) = 3.84, p = .02, \eta^2 = .067$. Post hoc tests indicated that the condition main effect reflected lower pain ratings during the computer game task ($M = 5.1$, S.D. = 4.5) compared to either the first ($M = 6.8$, S.D. = 5.9) or second ($M = 6.4$, S.D. = 5.7) rest conditions. Post hoc comparisons also indicated that the group by condition interaction reflected lower pain during the first rest and the computer game task, but not the second rest period, for participants with a positive versus negative parental history of hypertension. There were no other significant effects.

6. Discussion

The current research found that, during resting conditions, there was no difference in nociceptive thresholds between the hypertensives and normotensives, or between normotensives at risk for hypertension, as indicated by a family history of hypertension, compared to those not at risk. These results are at odds with previous findings of higher NFR

thresholds in individuals at increased risk for hypertension (France et al., 2002; France and Suchowiecki, 2001; Page and France, 1997). Experiment 1 of the current study is the first to determine NFR thresholds in unmedicated hypertensives. Our findings are consistent with the notion that the NFR is not affected by blood pressure status.

In line with studies which have investigated NFR thresholds in normotensives at risk for hypertension compared to those not at risk (France et al., 2002; France and Suchowiecki, 2001; Page and France, 1997), Experiment 1 revealed no differences in pain ratings associated with noxious stimulation delivered during the NFR assessments during resting conditions in hypertensives compared to normotensives. However, in Experiment 2, individuals with a parental history of hypertension felt less pain than those without a parental history of hypertension, in two out of three NFR assessments. As such, the current findings are largely at odds with the majority of the hypertensive hypoalgesia literature that reported a relative hypoalgesia in hypertensives compared to controls (Ghione, 1996). These discrepancies may be attributable to the use of different pain paradigms in previous studies that examined noxious thermal (Sheps et al., 1992), electrical tooth pulp (Ghione et al., 1985; 1988; Guasti et al., 1996; 1998; Guasti, Cattaneo, et al., 1995; Guasti, Gaudio, et al., 1999; Guasti, Merlo, et al., 1995; Guasti, Zanotta, et al., 1999; Guasti, Zanotta, Diolisi, et al., 2002; Rosa et al., 1994; Vignocchi et al., 1989; Zamir and Shuber, 1980), and electrocutaneous (Rosa et al., 1994) pain. These studies also employed a variety of pain assessment procedures, based on subjective pain thresholds, tolerances and pain ratings (see Ghione, 1996). In the current study, the NFR threshold assessments were, on average, rated 26.3 to 43.9 on a 0-100 scale, with anchors of 0 (no pain) and 100 (worst possible) pain, and therefore the electrocutaneous stimulation was rated as moderately painful. It is possible that the use of retrospective pain reports, which may be criticised for their vulnerability to memory distortion, may explain the absence of differences in pain between hypertensives and normotensives. A more likely explanation, however, is that the current study was designed to investigate NFR thresholds rather than pain thresholds, and therefore subtle differences between hypertensives and normotensives in pain could have been missed in this NFR paradigm.

It is important to note that hypertensive hypoalgesia has never been reported in hypertensives using the NFR paradigm. However, France and colleagues have noted higher NFR thresholds, but not retrospective pain ratings, in young normotensives with a parental risk for hypertension compared to controls (France et al., 2002; France and Suchowiecki, 2001; Page and France, 1997). Although these NFR studies were similar in many ways to the present study, the contradictory results reported by Page and France (1997) and France and Suchowiecki (2001) may be explained by a more stringent definition of the NFR: electromyographic activity at least 1.65 SD above baseline resting activity was used to define the occurrence of a reflex. While the current study and France et al. (2002) used a 1.5 SD definition for defining the NFR, mean resting NFR thresholds were higher in the study by France et al. (2002) compared to those found in the current study (positive parental history group: 22.1 vs. 11.8 mA, negative parental history group: 16.2 vs. 12.9 mA, respectively). Overall, it is evident that these previous NFR studies used higher stimulation levels than the current study. In conclusion, it is possible that hypertensive hypoalgesia may be more evident at higher stimulation intensities.

The Tetris[®] computer game task was used in the present experiments to change activation of descending pain modulation pathways. It has been proposed that enhanced supraspinal pain modulation may explain hypertensive hypoalgesia (France and Ditto, 1996). Tetris[®] is a complex visuospatial motor co-ordination task that has been shown to be as distracting and arousing as mental arithmetic compared to rest (Edwards et al., 2003b). In the current study, the threshold for eliciting NFR responses was lower during the performance of the computer game (i.e., the nociceptive flexion reflex was facilitated) compared to quiet sitting in both experiments, regardless of blood pressure group. The finding of lower NFR thresholds during

Tetris[®] computer game play compared to rest has been reported in a preliminary study in young healthy normotensives adults (Edwards et al., 2003b). In addition, other secondary tasks have been shown to facilitate NFR responses, including tasks which ask participants to search for differences between two pictures (Bathien and Morin, 1972), look at unpleasant pictures (Rhudy et al., 2005), or solve mental arithmetic problems (e.g., Edwards et al., 2006; McIntyre et al., 2006; Petersen et al., 2001). In contrast, early studies reported that secondary tasks, selected to be distracting and/or arousing, attenuated the NFR (Bathien, 1971; Bathien and Hugelin, 1969; Bathien and Morin, 1972; Willer et al., 1979). It is worth noting, in contrast to the present study which included 63 and 115 participants in Experiments 1 and 2 respectively, many of the early NFR studies employed small samples. Given that the likelihood of a type I error is increased with a small sample size (Oakes, 1987), some of the confusion in the literature could derive from the early studies testing less than 20 participants. Finally, it is worth noting that secondary tasks have been shown to facilitate the nociceptive blink reflex (Koh and Drummond, 2006) as well as other spinal reflexes such as the tendon reflex (e.g., Bonnet et al., 1995) and the stretch reflex (e.g., McIntyre et al., 2004).

Experiment 1 was the first attempt to assess the impact of engaging the supraspinal pathways involved in the modulation of activity in nociceptive neurons at the spinal level in hypertensives compared to normotensives. The finding that NFR thresholds were similarly reduced by Tetris[®] in both hypertensives and normotensives suggests that nociceptive responding is modulated in the same way in both groups, and therefore, the supraspinal descending modulatory system is functioning normally in hypertension. Furthermore, Experiment 2 corroborated this finding in a comparison of young normotensives at high versus low risk for hypertension.

The current study also found differences in NFR thresholds between the first and second rest whereas pain ratings did not differ between the rests. In both experiments, NFR thresholds were higher in the post-Tetris resting assessment compared to the pre-Tetris assessment. This finding concurs with a previous study that reported higher NFR thresholds post-math compared to pre-math (France et al., 2002). The mechanism underlying this phenomenon is unclear. Although it is possible that the distraction/arousal associated with the Tetris task may still be exerting some influence on nociceptive transmission even after the termination of the task, it is more likely that the small increase in NFR thresholds with repeated testing reflects habituation to sural nerve stimulation (see French, France, France and Arnott, 2005). It should be noted, however, that the NFR thresholds during the first rest were significantly correlated with the NFR thresholds during the second rest in the current study ($r = .93$ in Experiment 1 and $r = .84$ in Experiment 2) indicating high test-retest reliability.

The attenuation in *pain* during the performance of Tetris[®] compared to rest, found in both experiments of the current study, indicates that the computer game successfully engaged the supraspinal modulatory pathways associated with pain modulation. The current results are in accordance with a substantial body of evidence documenting that pain is reduced by distraction (al'Absi and Rokke, 1991; Flor et al., 2002; Miron et al., 1989; Petrovic et al., 2000; Villemure and Bushnell, 2002) and arousal (Maixner, 1991). That pain reports were not differentially modulated in both studies suggests that the central pain modulation pathways may not be altered as a function of blood pressure status or genetic risk for hypertension.

The absence of pain assessment in most previous studies of NFR modulation has precluded investigation of whether the pattern of modulation effects is similar for the two types of responses. It might be expected that a reduction in pain would be paralleled by an attenuation in NFR responding, i.e., higher NFR thresholds. However, the reduction in reported pain during the Tetris[®] task in both experiments in the present study was not paralleled by increases in NFR thresholds that would have reflected dampened nociceptive responding. Instead, the

opposite was observed. Specifically, the NFR was facilitated by the distracting and arousing computer game task, Tetris[®], while pain was attenuated. Such a dissociation between pain and the NFR has been noted previously (e.g., Andersen et al., 1995; Bouhassira et al., 2003; Edwards et al., 2001, 2002, 2003a, 2006; McIntyre et al., 2006; Terkelsen et al., 2004; Willer et al., 1979). In addition, a similar dissociation has been recently reported between pain and the nociceptive blink reflex during psychological arousal (Koh and Drummond, 2006). However, given that the attenuated NFR thresholds in the computer game task condition in the present study meant that lower intensity electrocutaneous shocks were delivered, reports of less pain are most likely to be, at least to a large extent, an artefact of reduced stimulation intensity. However, the pain modulation during Tetris persisted after adjusting for variations in electrocutaneous stimulation intensity across conditions, suggesting that the modulation effects observed for pain cannot be fully accounted for by variations in stimulus intensity. These results for the pain ratings are in agreement with three recent studies which found that the pain associated with noxious sural nerve stimulation was reduced during mental arithmetic compared to rest (Edwards et al., 2006; McIntyre et al., 2006; Terkelsen et al., 2004). Although the reason for such dissociation between pain and nociception is unclear, it is possible that increased psychological load may facilitate withdrawal responses while inhibiting sensory processing to promote an escape or flight response (for review see Keay and Bandler, 2001). In line with this hypothesis, a preliminary study which reported a dissociation between pain and nociception also reported an increase in arousal and distraction during the Tetris task (Edwards et al., 2003b). Regardless of the mechanism, the dissociation between NFR thresholds and pain during a distracting and arousing computer game task, suggests that these two types of responses are not influenced in the same way by psychological factors, i.e., distraction and arousal. Taken together these findings indicate that during conditions of increased psychological load the NFR threshold is not a suitable correlate of pain.

In an extension of McCubbin's (1991; 1993) model of central opioid insensitivity in the etiology of hypertension, France and Ditto (1996) proposed a model in which hypertensive hypoalgesia could be explained by one or more of three putative mechanisms: opioid dysfunction, baroreflex activation and enhanced activation of descending pain modulation systems. In humans, the evidence in favour of opioid dysfunction is mostly negative (e.g., Bruehl et al., 2002; France et al., 2005; Ring et al., 2007; Schobel et al., 1998; cf. McCubbin and Bruehl, 1994; McCubbin et al., 2006) whereas the evidence for baroreceptor activation is more mixed (e.g., al'Absi et al., 2005; Edwards et al., 2001, 2003a; Guasti, Zanotta, Mainardi, et al., 2002; McIntyre et al., 2006; Rau et al., 1995). Although the current experiments were designed to investigate the function of the descending pain modulation systems in essential hypertension and risk for hypertension, results indicated that there were no differential effects on nociception or pain. Future studies might wish to further explore the role of pain modulation processes using other pain paradigms, other tasks to activate the pain modulatory systems, and brain imaging methodology to determine the involvement of the brain structures in pain and nociception in hypertension.

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Table 1

Mean (S.D.) systolic blood pressures (SBP), diastolic blood pressures (DBP), heart rates (HR) and demographics of the hypertensive and normotensive groups in Experiment 1.

Variable	Blood Pressure Group	
	Hypertensive	Normotensive
Ambulatory (Daytime)		
SBP (mmHg)	149.5 (8.5)*	127.7 (9.5)
DBP (mmHg)	94.4 (9.1)*	78.6 (7.4)
Laboratory		
SBP (mmHg)	148.9 (14.3)*	122.7 (16.6)
DBP (mmHg)	89.5 (10.4)*	74.6 (10.2)
HR (bpm)	76.8 (11.6)	73.0 (8.1)
Sex		
Male	21	12
Female	14	16
Body Mass Index (kg/m ²)	26.1 (3.4)	26.2 (4.4)
Age (years)	45.5 (13.6)*	37.4 (13.4)

* significant difference between groups

Unadjusted mean (S.D.) nociceptive flexion reflex thresholds and short-form McGill Pain Questionnaire scores during rest and distraction conditions for the hypertensive and normotensive groups in Experiment 1, as well as the statistical significance level of the group, condition, and group by condition effects. Nociceptive flexion reflex threshold was used as a covariate in the analyses of the short-form McGill Pain Questionnaire scores.

Table 2

Variable	Group				Significance Level		
	Hypertensive		Normotensive		Group Effect	Condition Effect	Group by Condition Effect
	First Rest	Task	Second Rest	First Rest	Task	Second Rest	p
NFR Threshold (mA)	16.8 (10.5)	14.5 (10.7)	18.3 (11.0)	14.4 (7.8)	13.3 (7.9)	15.9 (8.3)	.61
Total Pain Rating Index (0–45)	6.4 (4.8)	4.3 (3.8)	5.8 (4.6)	8.1 (4.7)	5.3 (3.7)	7.5 (4.5)	.08
Overall Pain Rating (0–100)	37.8 (23.8)	26.3 (20.2)	38.9 (24.0)	43.9 (23.1)	32.5 (19.6)	43.8 (23.4)	.12
							.0001
							.001
							.001

Table 3

Mean (S.D.) systolic blood pressures (SBP), diastolic blood pressures (DBP), heart rates (HR) and demographics of the positive parental history of hypertension and negative parental history of hypertension groups in Experiment 2.

Variable	Blood Pressure Group	
	Positive Parental History of Hypertension	Negative Parental History of Hypertension
Laboratory		
SBP (mmHg)	112.9 (26.6)	113.8 (9.0)
DBP (mmHg)	65.1 (14.8)	66.7 (6.9)
HR (bpm)	69.2 (18.9)	72.6 (10.2)
Sex		
Male	31	38
Female	15	31
Body Mass Index (kg/m ²)	25.1 (3.6)	24.0 (3.6)
Age (years)	19.5 (2.2)	19.5 (1.6)

Unadjusted mean (S.D.) nociceptive flexion reflex thresholds and short-form McGill Pain Questionnaire scores during rest and distraction conditions for individuals with and without a parental history of hypertension in Experiment 2, as well as the statistical significance level of the group, condition, and group by condition effects. Nociceptive flexion reflex threshold was used as a covariate in the analyses of the short-form McGill Pain Questionnaire scores.

Table 4

Variable	Group				Significance Level			
	Parental History Positive		Parental History Negative		Group Effect		Condition Effect	
	First Rest	Task	Second Rest	First Rest	Task	Second Rest	p	p
NFR Threshold (mA)	11.8 (8.7)	11.6 (9.3)	13.5 (9.9)	12.9 (5.5)	11.4 (5.9)	13.7 (6.2)	.79	.0005
Total Pain Rating Index (0–45)	6.4 (5.9)	4.6 (4.5)	6.6 (5.7)	7.3 (5.5)	5.6 (4.2)	6.2 (5.3)	.60	.01
Overall Pain Rating (0–100)	33.2 (22.1)	29.7 (21.8)	33.7 (22.3)	42.2 (20.9)	36.4 (20.7)	38.4 (21.1)	.08	.01
								.35