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Contingent negative variation and cognitive performance in hypotension

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Abstract

The difference in attention and cognitive performance between 26 hypotensive (systolic blood pressure < 100 mmHg and diastolic blood pressure < 60 mmHg) and 22 normotensive female university students was assessed. Attention was examined with contingent negative variation (CNV) recorded using light and tone as S1 and S2. Cognitive performance was assessed by free recall of a list of words and two German tests of cognitive speed performance and sustained attention: Zahlen-Verbindungs-Test and d2. The hypotensive participants demonstrated a lower increase in negativity on the CNV. Moreover, in the free recall test, hypotensive individuals remembered fewer words, in comparison with normotensive subjects. Scores for hypotensive individuals on the Zahlen-Verbindungs-Test and d2 were also lower. No difference was found in reaction times to imperative stimuli (S2).

Descriptors: Hypotension, Contingent negative variation, Cognitive performance

The purpose of this study was to investigate whether hypotensive as compared with normotensive subjects show a significant decrease in the cognitive functions of attention and memory. According to the WHO (Cadalbert, 1997; Schwab, Grönefeld, Hobbje, & Wittmann, 1985; World Health Organization, 1978), hypotension is defined as low blood pressure (BP) with a systolic reading under 110 mmHg for males and under 100 mmHg for females without regard to diastolic blood pressure. Most authors, however, agree that the diastolic reading should be under 60–70 mmHg (Pschyrembel, 1990; Weiß & Donat, 1982).

Three different forms of hypotension are known: (1) chronic or essential hypotension (independent of illness or pathology); (2) secondary (due to organ impairments, lesions, injuries, loss of blood or shock); and (3) orthostatic (caused by circulatory problems, which may result in dizziness, temporary loss of sight or fainting, when assuming a standing position). Although there is strong evidence for hypertension inheritance (Carmelli, Swann, & Rosenman, 1986), only one study has reported genetic influence (Streeten, 1987) with respect to orthostatic hypotension.

The present study focuses on the clinical form of hypotension classified as "constitutional chronic hypotension II." The typical symptoms, according to Weiß and Donat (1982) are as follows—general symptoms: difficulty waking up in the morning, tiredness, sleepiness, lack of motivation, and reduced concentration; heart-blood circulation symptoms: palpitations, chest pain, cold hands and feet, headaches, dizziness, habitual paleness; gastrointestinal symptoms: loss of appetite; respiratory symptoms: breathing difficulties.

Other studies have reported symptoms such as dizziness, giddiness, and coldness (Christian, Kropf, & Kurth, 1964; Kerekjarto, 1973; Pemberton, 1989; Pennebaker, 1982; Pilgrim, Stansfeld, & Marmot, 1992; Schwab, 1992; Wessely, Nickson, & Cox, 1990; Wittmann, 1989). Other investigations have also identified psychological lability, emotional problems, in particular greater neuroticism and higher levels of depression (Davies, 1970; Oberleiter, 1985; Schalling & Svensson, 1984). Hypotension has received little attention in medical research, in comparison with hypertension, because it is not considered a health risk for cardiovascular morbidity. Nevertheless, from a social point of view, hypotension is not irrelevant. In a study conducted by the Kiel Institute for Health and Research and reported by Boschke (1982) a total of 2.45 million hypotensive individuals were found in Germany, in 1979. In 1978, again in Germany, there were 632,000 cases of work absence that were medically certified on the bases of hypotension: the women-men ratio was 2:1. Hence, the social cost of hypotension appears to be substantial (see also Girstenbrey, 1982).

In a study by Stegagno, Angrilli, Costa, and Palomba (1996) that compared 17 hypotensive (mean systolic BP: 96, mean diastolic BP: 55.8) with 19 normotensive individuals (mean systolic: 118.4, mean diastolic: 67.5), the investigators searched for differences in cognitive performance, oral temperature, and startle re-

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flex, as well as circadian trends. Among the findings of this study were the following:

1. Oral temperature was significantly 0.37 degrees lower in hypotension, compared with normotension (mean: 36.01°C for hypotensive individuals and 36.38°C for normotensive individuals).
2. Hypotensive individuals demonstrated a significantly greater startle reflex (startling stimuli were presented 0.5 s after a neutral slide).
3. In a free recall test of a list of 16 words (Baddeley, 1982), hypotensive subjects displayed significantly poorer memory performance in comparison with normotensive subjects.
4. On the Descending Subtraction Test the mean score of hypotensive individuals was significantly lower in comparison with that of the normotensive group.
5. No significant differences were found between the two groups for simple reaction times to acoustical stimuli nor for a digit-span measure of short-term memory.

Evidence of a close relationship between blood pressure and cortical activity derives from the studies that investigated the cortical contingent negative variation (CNV) during baroreceptor activation (Elbert, Roberts, Lutzenberger, & Birbaumer, 1992; Koch, 1932; Rau et al, 1988; Rau, Pauli, Brody, Elbert, & Birbaumer, 1993; Vaitl & Gruppe, 1990, 1992). In general, these studies indicate that baroreceptor activation (phasic blood pressure increase) is associated with reduced CNV. Moreover, Elbert et al. (1988) and Larbig, Elbert, Rockstroh, Lutzenberger, and Birbaumer (1985) showed reduced pain thresholds during baroreceptor stimulation in borderline hypertension, suggesting that cortical inhibition modulates information processing in hypertensive individuals. However, thus far, studies of cortical and behavioral responses in hypotensives have been scarce.

The aim of the current experiment was to provide stronger evidence with respect to poorer cognitive performance among hypotensive subjects. Specifically, we attempted to replicate previous finding for free recall. In addition, the CNV was chosen as a measure of distraction-attention (Tecce, 1972a, 1972b). To assess cognitive performance, we used two standardized and well-established tests developed in Germany: the Zahlen-Verbindungs-Test (ZVT, number connections test) (Oswald & Roth, 1987) for speed of cognitive performance, and the d2, Aufmerksamkeits-Belastung-Test (attentional load test) (Brickenkamp, 1994), to measure sustained attention and cognitive load. These two tests were introduced to assess differences between the two groups with complex, structured, and standardized tests that required more than simple subtractions and that allowed for comparison with the existing literature on differences in cognitive performance between normotension and hypertension. For this pathology, in fact, there is a long tradition of studies regarding poor performance in common tests of perception, psychomotor ability, learning and memory, attention, visuospatial skills, and general intelligence (e.g., Blumenthal, Madden, Pierce, Siegel, & Appelbaum, 1993; Boller, Vrtunski, Mack, & Kim, 1977; Franceschi, Tancredi, Smirne, Mercinelli, & Canal, 1982; Mazzucchi et al., 1986; Shapiro, Miller, King, Ginchereau, & Fitzgibbon, 1982; Waldstein, Ryan, Manuck, Parkinson, & Bromet, 1991).

CNV was chosen as a measure of attention—using the classic S1-S2 paradigm, with reaction times to imperative stimuli—on the basis of previous work in this area. Many studies have demonstrated the importance of distraction (whether caused by external or internal sources) as a powerful disruptor of CNV development (Tecce & Cattanach, 1987, 1993). Effects of different psychotropic drugs on CNV amplitude parallel their effects on attentional behavior. Thus, if a stimulus induces a subjective experience of alertness, it also induces increased CNV amplitude (Tecce, Savignano-Bowman, & Cole, 1978). In addition, when a subject expends a great amount of cognitive energy in anticipation of a task performance, the amplitude of CNV increases (Low & McSherry, 1968). In summary, CNV tends to be associated with an anticipated degree of psychological effort, and can thus be related to the subject's degree of motivation.

The following predictions were made: hypotensive individuals should show worse performance on the two cognitive tests, remember fewer words on the free recall test, have a lower increase in negativity, and a slower responses to imperative stimuli on CNV trials.

Method

Subjects

The subjects were 26 women with hypotension (mean age: 28.1 years; sd: 7.82) and 22 women who were normotensive (mean age: 25.1 years; sd: 4.27). We decided to focus exclusively on females in the present study because they are far more likely to be hypotensive. The subjects were university students recruited through advertisements and paid 15 DM. The CNV data from one hypotensive subject were discarded from the analysis due to technical problems during the recording phase. Subjects were told the purpose of the study was to investigate psychophysiological responses to perceptual stimuli using individuals differing in blood pressure.

Design

A repeated measures design was used with group as the between-subjects variable and repeated measures on the following dependent variables: (a) psychophysiological: CNV; (b) motor: reaction times to imperative stimuli in CNV trials; (c) cognitive: d2 and ZVT for mental speed, cognitive load, and attention, and a memory test that consisted of free recall of a word list.

Apparatus and Stimuli

The experiment was performed in a sound-attenuated room inside a laboratory. Temperature and light conditions were consistent for all subjects during the experiment. All physiological data for CNV were collected and amplified using Syn-Amps DC amplifiers controlled by NeuroScan software (version 3.2). A notch filter was used to eliminate 50-Hz interference.

CNV activity was recorded from the vertex (Cz) referred to linked mastoids (A1/2). Vertical eye movements were recorded from the left eye with one electrode placed below the eye and the other immediately above the eyebrow. Sampling rate was 1 kHz from 200 ms before the onset of S1 (red light) to 3,000 ms after the beginning of S1. The S1-S2 interval was 2 s whereas the intertrial interval was 6 s. The imperative stimulus S2 was a tone to which the subject had to respond as fast as possible, pressing a key held in the dominant hand. The data were digitally filtered online to a 0–70-Hz bandpass using a zero latency-shift filter (approximately −40 dB shoulders) (Cook & Miller, 1992). Trials with excessive voltages ($\pm$ 50 μV) were excluded from the averaging process.

Trials containing eye movements were corrected offline using the Semlitsch, Anderer, Schuster, and Presslich (1986) algorithm. Recording continued until a total of 50 sweeps had been obtained. Reaction times were collected using a Hewlett-Packard 5304A timer-counter. Presentation and timing of all stimuli were controlled on-line by a Massey-Dickinson control device. Electrodes were filled with Elefix paste and had impedances below 5 kΩ to minimize skin potential artefacts.

Blood pressure measurements were taken with a new manual sphygmomanometer (Speidel and Schneider, mod. 300-CE-0047) with a mercury column. The cuff (width 14 cm) was placed on the left arm at about 2.5 cm above the antecubital space and the diaphragm stethoscope was placed directly over the palpated brachial artery. We monitored blood pressure levels using phase I and phase V of Korotkoff sounds (Fröhlich et al., 1988). Because two experimenters were working on this study, before collecting actual data, they practiced until they reached a high level of interreliability ($r = .9$). To maintain consistency, all of the blood pressure readings for a particular subject were collected by the same experimenter. The interval between repeated measures was 2 min of rest without moving or speaking.

The free recall test (Baddeley, 1982) consisted of 16 words read by the same researcher followed by eight easy mathematical calculations to eliminate recency effects. The subject was then asked to write all remembered words, ignoring the order in which they were presented. The test ended when the subject was unable to recall any additional words.

The ZVT (number connection test) (Oswold & Roth, 1987), consists of 4 matrices of 90 numbers. The task is to mark the path from number 1 to 90 as fast as possible. Every subsequent number is close to the previous one and every number is inscribed in a circle. This test, which measures speed of cognitive performance independent of verbal ability, has shown a significant correlation with certain intelligence tests: Prüf-System für Schul- und Bildungsberatung (Horn, 1969), Intelligenz-Struktur-Test (Amthauer, 1970), Hamburg-Wechsler-Intelligenztest für Erwachsene (Wechsler, 1964), Standard Progressive Matrices (Raven, 1938), and Grundintelligenz-Test CFT 3 (Weiß, 1971). Furthermore, scores on the Zahlen-Verbindungs-Test correlate with academic performance and various tests of concentration, including d2, which was used in the current experiment.

D2 (Brickenkamp, 1994), the final measure of cognitive performance, requires the subject to identify all target stimuli (consisting of the letter “d” with two apostrophe marks). The apostrophe marks may be both above, both below, or one above and one below the d. Distracting stimuli are ds with one, three, or four marks or ps with one or two marks. All the stimuli are contained in 14 rows, each of which contains 47 letters. The subject is allowed to scan every row for 20 s. When the 20 s are up, the researcher tells the subject to move immediately to the following row.

Procedure

To divide subjects into normotension and hypotension groups and to assess chronicity, female volunteers were screened at least 1 week prior to the experimental session. After 10 min rest, we took three blood pressure measurements with a 2-min interval between each of them (Shapiro et al., 1996). If the mean was less than 105 mmHg for systolic and less than 65 mmHg for diastolic then the subject was placed in the hypotension group (both criteria had to be satisfied), whereas means higher than 110 mmHg for systolic BP and 70 mmHg for diastolic BP, placed the subject in the normotensive group. Individuals with diastolic BP greater than 90 mmHg were excluded because they would be considered hypertensive and subjects with systolic BP between 105 and 110 and diastolic BP between 65 and 70 mmHg were excluded because they were considered borderline.

All experimental sessions were conducted in the morning between 9:00 a.m. and 1:00 p.m., considering that blood pressure changes during the day (Pickering & James, 1993). Each subject received the following instructions before undertaking the experiment: Do not drink coffee and alcohol for 3 hr, do not smoke for at least 2 hr, do not take any drugs for 3 hr, and avoid salty food and licorice for breakfast.

At the start of the experimental session (after written informed consent was obtained) the subject was left alone for 15 min listening to relaxing classical music before three baseline blood pressure measurements were collected (Shapiro et al., 1996). Then the subject was seated in a reclining chair with headrest support in a test chamber that communicated via intercom with the adjacent room. Electrodes for CNV recording were applied.

The CNV recording consisted of a total of 50 trials: Each started with a red light followed, after 2 s, by a tone in response to which the subject had to press a key in the dominant hand as fast as possible. The intertrial interval lasted 6 s. After removing the electrodes, there was one blood pressure measurement (to determine if CNV trials changed the baseline values) followed by all three cognitive paper and pencil tests. The order of administration of the tests was counterbalanced across the subjects. The experimental session ended with a final blood pressure measurement to ensure that the hypotensive subjects still met the initial criterion for hypotension: systolic BP $<$ 105 mmHg and diastolic BP $<$ 65 mmHg (i.e., we wanted to rule out the possibility that our experimental conditions had significantly raised the blood pressure of the hypotensive subjects).

Data Reduction and Analysis

Continuous raw electroencephalographic (EEG) data were collected for CNV analysis starting 200 ms before S1 (warning light) and ending 1 s after S2 (tone) onset. Fifty sweeps were obtained. Trials containing eye movements were corrected using the Semlitsch et al. (1986) algorithm. The mean DC offset included from -200 to 0 ms was computed and subtracted from the whole wave for DC drift correction. Averaged CNV measures were obtained and slow wave amplitudes were measured by calculating the mean amplitude over seven points after S1 (500, 750, 1,000, 1,250, 1,500, 1,750, and 2,000 ms).

Recall scores on the memory test were computed in terms of the number of correct words reported, regardless of word order. For the ZVT, mean scores were computed over the four durations used by the subjects to connect the 90 numbers on the four matrixes. The mean speed was corrected in reference to age and standardized using the test-manual tables. For the d2 test, we first computed the total number of letters scanned by the subject, independent of the target-distractor classification. For every row, this procedure yielded a sum of the number of letters up to the last one identified as target. We then computed type I (missed targets) and type II (false positives) mistakes and subtracted this score from the total number of scanned letters. This raw score was then corrected in reference to age and standardized using the test-manual tables, to make the results comparable with ZVT scores.

In order to reduce the risk of falsely rejecting the null hypothesis, a single multivariate analysis of variance (MANOVA) was used to examine the dependent variables: CNV, reaction times, free recall, ZVT, and d2.

Results

A main effect of the difference between normotension and hypotension was obtained when the five dependent variables were collapsed: Rao's R (5,40) = 5.77, $p < .001$ (Wilks' Lambda = .58).

Blood Pressure

The mean systolic blood pressure was 117.55 (SD = 4.07) in normotensive individuals and 98.26 (SD = 4.79) in subjects with hypotension, with a difference of 19.29 mmHg, $F(1,45) = 218.40$, $p < .001$. The diastolic means were 72.30 (SD = 4.35) for normotensive subjects and 59.87 (SD = 4.22) for hypotensive subjects, with a difference of 12.43 mmHg, $F(1,45) = 98.68$, $p < .001$. Systolic blood pressure showed a significant change over the course of the experiment $F(2,90) = 3.76$, $p < .02$, $\epsilon = 0.95$. Post hoc analysis with Tukey's HSD test revealed a deflection after the psychophysiological trials ($p < .05$) and a return back to baseline levels ($p < .04$), after the cognitive paper and pencil tests. Diastolic blood pressure did not show any significant change. The interaction involving group and systolic changes was not significant, $F(2,90) = 1.40$, $p < .25$. The significant changes, however, were in mean from 107.90 to 106.37 and then again to 107.93 mmHg. Ultimately the difference was only 1.5 mmHg so the two groups remained strictly distinct. No significant changes during the experiment were found for diastolic blood pressure.

CNV

The CNV analysis revealed a larger increase in negativity in normotensive subjects (-4.51 μV) than in hypotensive subjects (-1.34 μV), $F(1,44) = 6.05$, $p < .02$. Figure 1 depicts the CNV grand-averages for all the subjects within the two groups. S1 was the warning stimulus (light) and S2 the imperative stimulus (tone). The imperative stimulus was present in all trials.

Reaction Times

During the CNV trials, no significant difference in reaction times was found between the two groups. The mean speed for hypotensive subjects was 345 ms versus 358 ms for normotensive subjects, $F(1,45) = 0.42$, $p > .41$.

Free Recall

The mean number of correct words remembered by normotensives was 8.50, whereas the number recalled by hypotensives was 7.08. This difference between the two groups was significant, $F(1,45) = 4.98$, $p < .03$.

ZVT (Number Connection Test)

With both of the cognitive paper-and-pencil tests, the difference between groups was highly significant. In the ZVT, the mean score for hypotensive individuals, in terms of standardized scores, was 102.44, whereas for normotensive individuals the mean was 111.82, $F(1,45) = 13.13$, $p < .001$.

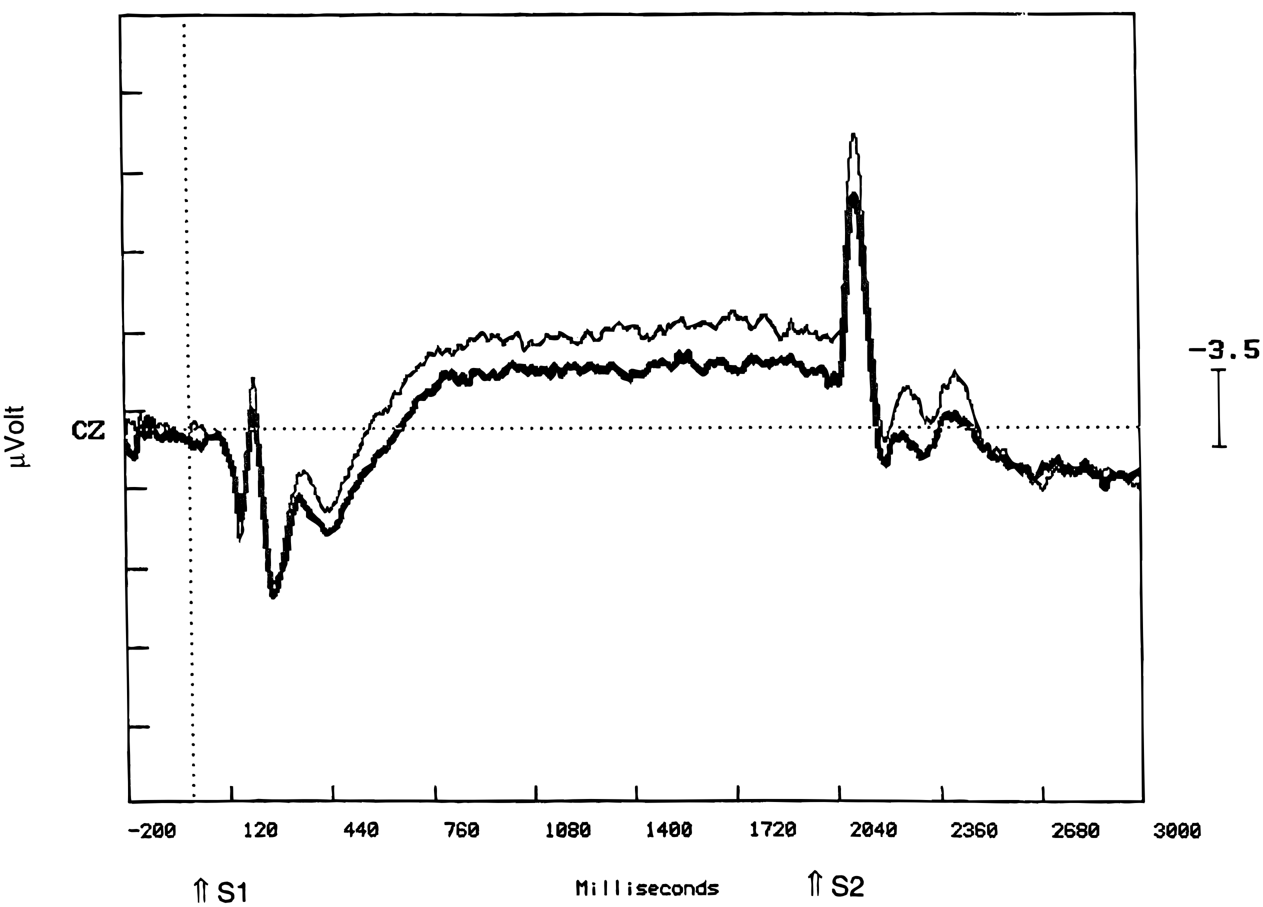

Figure 1. Grand-averages of contingent negative variation in normotensives (light line) and hypotensives (dark line). S1 was a light (warning stimulus) and S2 a tone (imperative stimulus).

d2

The mean d2 score (again in terms of standardized scores) was 111.88 for hypotensive and 119.77 for normotensive subjects, $F(1,45) = 8.77$, $p < .005$. The mean values for the d2 test were higher compared with the ZVT scores. However, the size of the difference between normotensive and hypotensive subjects was similar across the two cognitive tests (9.38 and 7.89, respectively). The coefficient of correlation between the two cognitive tests was high: $r = .63$, $p < .05$. Figure 2 illustrates the comparison between normotensive and hypotensive subjects with respect to the two cognitive tests. Figure 3 shows the scatterplots in function of mean blood pressure.

Discussion

A substantial difference in cognitive performance was measured between chronic hypotensive and normotensive individuals. Subjects with chronic low blood pressure performed worse on both cognitive paper-and-pencil tests, remembered fewer words, and had a lower increase in negativity on the CNV. These results are in accordance with a previous experiment by Stegagno et al. (1996). No significant difference was found for reaction times to imperative stimuli in CNV trials. Rebert and Tecce (1973), after a careful review of the available literature, concluded that CNV and reaction times are relatively independent factors and that the relationships that had been reported in some studies resulted from experimental manipulations and did not reflect a strong causal relationship between the two processes. Also, in Stegagno et al. (1996), reaction time for the two blood pressure groups did not vary significantly as

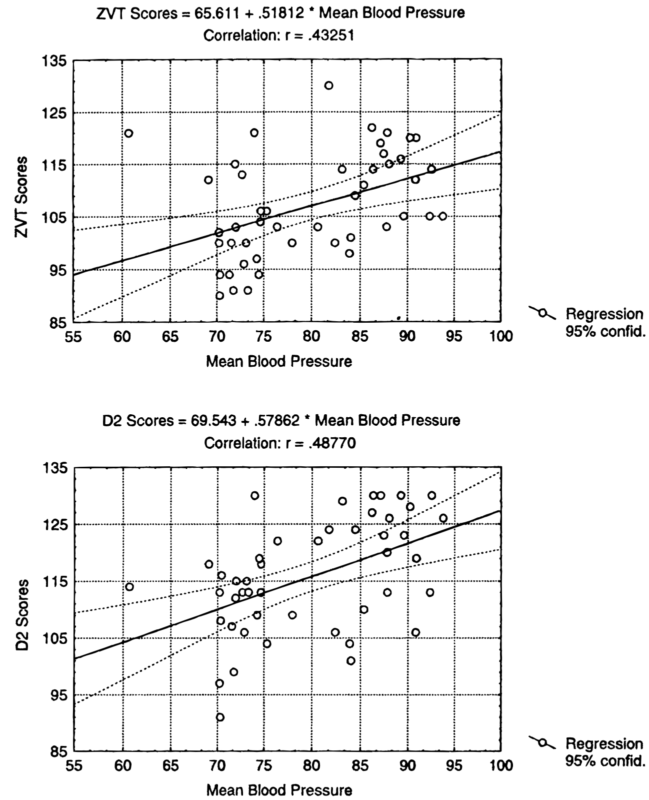

Figure 3. Scatterplots for ZVT and d2 tests in relation to mean blood pressure.

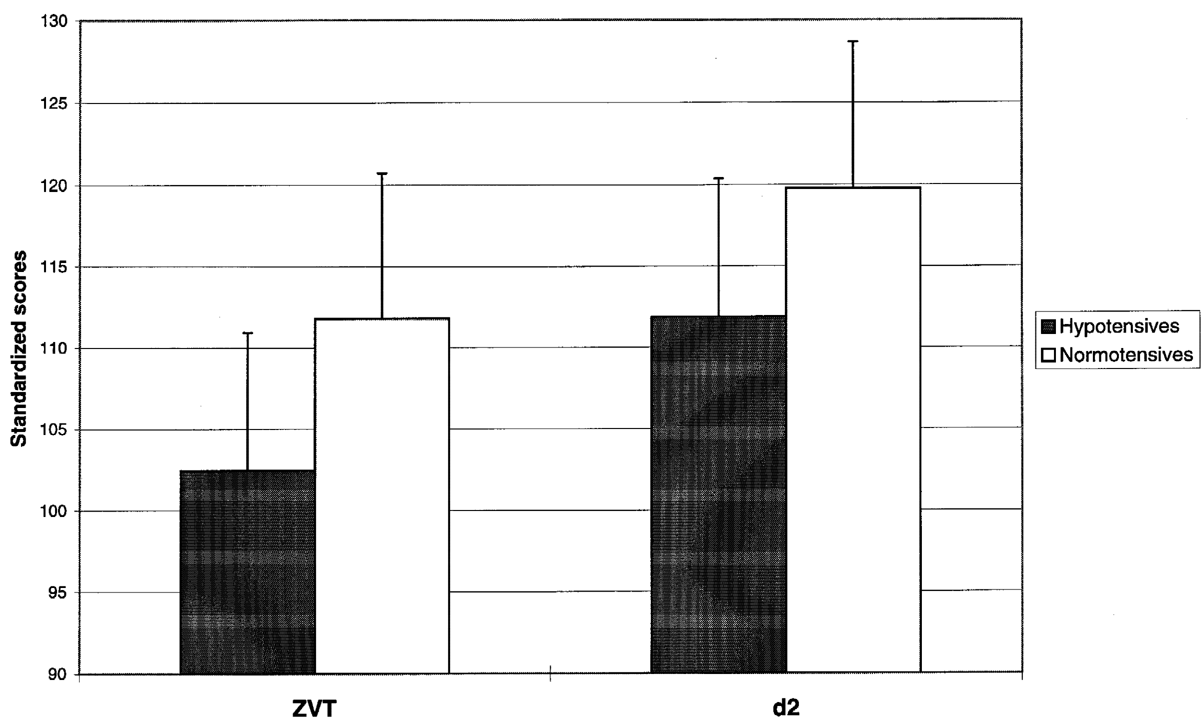

Figure 2. Comparison between hypotensives and normotensives for the two cognitive tests ZVT and d2. Scores are in terms of standardized values. Error bar represents standard deviation.

a function of acoustic stimuli. According to McCallum (1988): “It is possible that the CNV reflects not the absolute speed of response but the gain, i.e., improvement in speed, achieved by virtue of the presence of the warning stimulus, as compared with an unwarned response” (p. 467). It is conceivable that simple reaction time is too easy a task (too undemanding of resources) and, consequently, results in a floor effect. However, we must take into account that the S1-S2 interval of 2 s did not allow for discrimination between an early and a late component on CNV development and it is possible that the CNV difference between hypo- and normotensive individuals might be different for the two CNV components, and the CNV–reaction times relation might be apparent considering the distinct components.

The negativity shift in CNV is slow and typical for a Type B-shaped CNV (Tecce, 1971, 1972a, 1972b) given there was no uncertainty as to the appearance of S2 and that the interstimulus interval was always the same. The difference in negativity between the two groups becomes evident at 400–2,000 ms (presentation of S2). The normotensive CNV is more highly related to hypotensive individuals for the entire time. Because CNV has been related to attentional processes by many studies that deal with the distraction, the rebound, and drug effects (for a critical review see Rockstroh, Elbert, Canavan, Lutzenberger, & Birbaumer, 1989), the lower CNV may be viewed as supporting the hypothesis that some aspects of attentional processes are deficient in subjects with chronic low blood pressure. An alternative explanation might be that the disruptive effects on cognitive performance in hypotensive individuals may be attributed to distraction from internal sources because, in this case, external factors were well controlled (Tecce & Cattanach, 1993). If this is the case, the hypotensive individuals may have difficulty allocating cognitive resources to perform a main task. A criticism regarding this attentional explanation might be the vagueness of the concept of “attention” (Hillyard & Picton, 1979) but, according to McCallum (1988), “If slow potentials such as the CNV also relate to selective processes in attention, it seems likely that they are concerned less with the initial process of stimulus selection, as may be the N1 and P2, and more with sustaining a focus of awareness on a given configuration or succession of stimuli” (p. 447). It is to this latter concept of attention to which we refer when we discuss the hypotensive deficits.

On both the ZVT and the d2 test, hypotensive subjects performed worse than normotensive subjects, demonstrating lesser ability in conditions of sustained attention and slower cognitive speed. Because the sample was composed of university students, the score distributions (in particular for d2) are skewed in the positive direction. The grand mean for all the scores was 112.04 (standardized value). The correlation between the two tests was high: $r = .63$, which is to be expected from two tests that both measure the speed of cognitive performance. The free-recall results confirm the findings of the previous work by Stegagno et al. (1996), which revealed poorer performance for hypotensive subjects in memory tasks.

The results of this experiment may be combined with those that show a comparable decrement in cognitive functioning among hypertensive individuals (e.g., Blumenthal et al., 1993; Elias, Robbins, Schultz, Streeten, & Elias, 1987; Farmer, White, & Abbott, 1987; Madden & Blumenthal, 1989; Waldstein, Manuck, Ryan, & Muldoon, 1991). This study and others have focused on basal or chronic levels of blood pressure, rather than phasic changes. In such individuals, cognitive differences could perhaps be attributed to brain alterations due to protracted exposure to pathological blood pressure levels. Pathophysiology-based explanations of the link between hypertension and cognition have, for instance, been widely accepted, and support comes from various studies that suggest a malfunctioning of the baroreceptors (e.g., Elbert et al. 1992; Rau et al., 1993) and others that show a link between white matter lesions and cognitive deficits in elderly hypertensives (e.g., van Swieten, Geyskes, & Derix, 1991). The neurobiological basis of cognitive impairment, however, might be different between hypertension and hypotension.

Now that some understanding of the relationships between hypotension and global cognitive performance has been achieved, future investigations have to prove if there is a causality between chronic low pressure and the cognitive impairments or if these consequences might be explained by a third variable such as a lower metabolic rate. In this sense it would be interesting to examine if there are alterations of the cerebral blood flow during cognitive tasks in these subjects. Additionally, the particular mental processes that are affected by chronic low blood pressure have to be clarified. To achieve this goal, we will need to apply established measures of information processing in a more analytic fashion. Global measures, such as those used here, do not permit analyses at the level of specific information processing tasks, such as, for instance, Sternberg’s paradigm for studying short-term memory (Sternberg, 1969). Global measures of learning, cognitive speed, or other mental operations or processes, almost always involve multiple and inseparable components. In this sense, studies of global cognitive deficits in hypertensive and hypotensive subjects may be inadequate because such impairments can rise from a variety of processes or at different stages within the same process.

To determine whether cognitive deficits result only from chronic low blood pressure or can occur in the presence of phasic changes, it would be important to ascertain if cognitive performance varies with experimentally induced changes in blood pressure levels. For example, it could be examined whether cognitive impairments disappear when hypotensive subjects are given drugs or engage in activities that raise their blood pressure. Alternatively, whether cognitive impairments appear in normotensive subjects if their blood pressure is lowered, for example, via drugs that have no direct effect on cognitive performance, would be an alternate route of investigation.

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