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Research Article

Hemodynamic changes in the prefrontal cortex during working memory in essential hypertension

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Abstract

Behavioral performance and hemodynamic changes in the prefrontal cortex (PFC) represent cerebrovascular reserve and may indicate functional deficits related to essential hypertension. Fifteen stage 1 hypertensive and normotensive males (19–55 years) were compared on four tests of working memory (digit span and auditory consonant trigrams), and accompanying hemodynamic changes measured by functional near infrared spectroscopy (fNIRS). With participants blindfolded, the four tests were randomized while fNIRS was used to monitor bilateral PFC changes in oxyhemoglobin (O_2Hb), deoxyhemoglobin (HHb), total hemoglobin (tHb), and hemoglobin difference. The hypertensive group demonstrated significant impairment in performance on the working memory tests with a trend of decreased efficiency performance scores (tests score/O_2Hb and tHb changes). Significant correlations were noted in the hypertensive group between test performance and changes in O_2Hb and tHb in both the left and right PFC. These findings suggest that fNIRS combined with cognitive testing may provide important measures of cerebrovascular reserve in essential hypertension. J Am Soc Hypertens 2015;■(■):1–12.

Keywords: Hemodynamic; hypertension; near infrared spectroscopy; prefrontal cortex.

Introduction

An association between hypertension and decreased cognitive function in adult populations has been reported over the past several decades.[1] More recently, decreased cognitive performance has also been noted in school-aged children with above normal blood pressure (BP) readings.[2] Changes in cerebrovascular physiology caused by the disease are potential explanations for the association between hypertension and diminished cognitive performance. In this regard, a decrease in circulatory efficiency in adjusting to cognitive performance is a measure of the cerebral vasodilatory reserve. Such a phenomenon may be defined as active modifications within the cerebrovascular system, through neurovascular coupling, to appropriately accommodate the blood flow needs. Changes in cerebrovascular hemodynamic efficiency may be a direct result of the hypertensive small vessel disease process, such as the thickening of the arterial endothelium and narrowed lumen.[3] The nexus between neurovascular changes in hypertension and cognitive function, in the form of working memory, is highly appropriate for examination of the association between hypertension and cognitive performance.

Working Memory

The ability to resist distractions and avoid impulsive behavior, integral to functional working memory, is the foundation of "executive function." The phonological

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Informed consent: The procedures of this study were fully in accordance with the Helsinki Declaration 1975 on ethical standards for human experimentation and its revisions at the time of testing. All participants gave informed consent for inclusion in the study.

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loop, a central concept in working memory as per Baddeley,[4] involves a brief storage of verbal information with a rehearsal mechanism in service of healthy brain function. Such a mechanism is integral to control over one's attention, planning, and problem solving; that is, executive capabilities.

Necessarily, testing phonological working memory is an important part of the neuropsychological clinical workup in evaluating cognitive function. The digit span task, Wechsler Adult Intelligence Test (WAIS IV),[5] is part of such an assessment and has been used in brain activation studies to evaluate conditions as varied as schizophrenia, Alzheimer's disease, and Parkinson's disease.[6–8] However, none of these studies have investigated altered brain activation patterns during increasing cognitive load.[9] To our knowledge, specifically loading of the digit span task with other neuropsychological tests has not been previously used to evaluate working memory.

The auditory consonant trigrams (CCC), also known as the Brown–Peterson procedure, is a neuropsychological test designed to evaluate working memory and divided attention capacity.[10] These elements of healthy brain function have been reported to be deficient in hypertensives.[11] The CCC presents a brief distraction while requiring retention of information,[12] a necessity in normal daily activity. Researchers report that CCC is particularly sensitive to changes in the frontal lobe including deficits in information processing.[13,14]

The prefrontal region, important in executive function, atrophies more readily in hypertensive patients, when compared with other regions of the brain, and to the brain of normotensives.[15,16] However, Kupferman et al[2] suggest that hypertension impairs mainly elemental memory processes. Prefrontal cortex (PFC) morphological changes, supported by growing evidence of decreased executive function as a feature of the disease,[1] demand closer scrutiny. To our knowledge, an assessment of PFC hemodynamic changes and performance in hypertension while performing CCC and the digit span test has not been done.

Assessing Hemodynamic Function in Hypertension

The neurological substrates that support the cerebral changes accompanying hypertension are complex. Nonhuman experimental data[17] and information from human neuroimaging correlational research propose that hypertension might influence the PFC earlier and more extensively than other regions of the brain.[16] Strongly associated with activity in the PFC are information processing, attention and recall,[14] essential components of working memory, which are tested by both the digit span task and the CCC.

The hemodynamic changes in the PFC accompanying these tests of working memory can be evaluated by functional near infrared spectroscopy (fNIRS). This technique uses near infrared light (700–1300 nm) over the cranium to measure changes in concentration of cortical oxyhemoglobin (O_2Hb) and deoxyhemoglobin (HHb) that accompany the neuronal activity coinciding with the cognitive task(s).[18,19] The results of this neuroimaging approach are highly correlated with those of functional magnetic resonance imaging (fMRI) in assessing superficial cortical activity ($R = 0.98$).[20,21] fNIRS is known to have high temporal resolution and is highly adaptable to test situations while adequately evaluating hemodynamic brain function during cognitive testing.[19,22]

Prefrontal activation studies using fNIRS, in healthy populations, report conflicting results on digit span testing.[22,23] Using repetitive transcranial magnetic stimulation, Aleman and van't Wout[24] reported that the right PFC was important in better performance on the digit span task. However, an earlier study using fMRI[25] reported greater activation in the left PFC on the digit span backward task (DSB). Similar hemodynamic testing in hypertension groups has not been done, and the unique microvascular changes of PFC oxygenation and laterality that might accompany the disease are unexplored. Moreover, no meaningful comparisons can be made between hypertensive and healthy populations. Thus, the functional deficits associated with hypertension are poorly elaborated, and the theoretical foundation for therapeutic intervention, where necessary, is not robust. To advance the discussion, this study assessed behavioral performance and PFC hemodynamic changes in an essential hypertensive population, devoid of comorbidities, who are arguably experiencing their most active and productive years (55 years and younger).

Hypotheses

We hypothesized that (1) performance on the working memory tests would be significantly impaired in the hypertensive compared with the normotensive participants; (2) indicative of impairment in performance efficiency in hypertension, the changes in PFC O_2Hb, and total hemoglobin (tHb), an estimate of blood volume changes, would be significantly higher in the hypertensive during testing; (3) there would be significant differences between the right and left PFC for blood volume changes (tHb) during the working memory tests in both groups; (4) the changes in O_2Hb and tHb would be significantly correlated with working memory performance in both groups.

Methods and Procedures

Participant Recruitment

Study participants included normotensive and stage 1 essential hypertensive males between 19 and 55 years old. The hypertensive group had an explicit diagnosis of uncomplicated stage 1 hypertension with no known comorbidities

as determined by their Alberta registered family physician. They were recruited from the University of Alberta, health clinics, and community organizations in the wider Edmonton, Alberta community. Only males were recruited for this study to avoid issues regarding gender and cerebral hemodynamics.[26,27] Use of antihypertensive medication did not preclude participation in the study, and the BP of all participants was deemed ''controlled'' by their physician for more than 6 months before the date of testing.

Tests and Procedures

Procedures of testing were approved by Health Research Ethics Board, University of Alberta. After providing written informed consent 1 day prior, all participants were instructed to avoid a heavy meal for more than 4 hours and to refrain from caffeinated drinks for at least 2 hours before testing. Participants arrived approximately 1 hour before test time for procedure instructions. They were encouraged to ask questions about the study and advised of their right to stop the test at any time without repercussions. The participants were also advised of a posttest interview and debriefing to answer questions about the test.

After the initial instructions, participants' weight, height, cranial circumference, resting heart rate, and BP[28] were measured, along with completion of the Beck Depression Inventory II.[29] If no signs of depression were identified (Beck Depression Inventory II score >13 for this study), the participant would then be oriented to the equipment by the examiner. The typical testing period lasted approximately 75 minutes and occurred between 2 PM and 6 PM Mountain Standard Time. All testing was performed by the same examiner.

The working memory tests, conducted in sitting, consisted of the three-part digit span task and the CCC which were randomly ordered and counterbalanced. Resting BP was monitored before and after testing using the auscultatory method at the left arm in a sitting position. (The BP reading used was an average of three measures over 5 minutes for before and after memory testing.) Heart rate was monitored throughout testing with a wireless monitor and chest strap (Polar Global 100, Finland). The examiner encouraged all participants to give their best effort. However, aside from confirming that test instructions were understood with a brief trial for each test, no attempt was made to coach participants on the use of memory or recall strategies.

The Digit Span Task

The digit span task is comprised three parts (Wechsler Adult Intelligence Test IV): the digit span forward task (DSF), the digit span backward task (DSB), and the digit span sequencing task (DSS). All parts of the test procedure, including stopping rules and scoring, were followed as per the test manual.[5] In the DSF, the examiner reads aloud a number, increasing in digit span, starting with two digits and comprising two numbers per sequence, up to a total of eight sequences. The number of digits in each sequence is progressively lengthened and concluding at the eighth sequence. The participant is asked each time to repeat aloud the numbers in exact order as told by the examiner. The stopping rule is that a participant will not continue with the DSF if he gives two incorrect answers in the same sequence or if he completes all eight sequences. One point is issued per correct response given by the examinee for a potential total of 16 points. Similarly, the DSB consisted of eight sequences of two numbers of increasing digit span. In this task, the participant is asked to respond with an exact reverse order of the digits spoken by the examiner. The stopping and scoring rules were the same as for the DSF. The DSS also included eight sequences of two numbers of progressively increasing digit span. The instructions were that the participant should reorder the digits spoken by the examiner starting with the lowest number and repeat the digits to the examiner in ascending order. The stopping and scoring rules were as for the other parts of the digit span task.

The Auditory Consonant Trigrams

In the CCC, the examiner spoke three random consonants to the participant who was then asked to count aloud and backward in three's from a specific number also given by the examiner.[12] After 9, 18, or 36 seconds of counting backward, the participant was stopped and asked to repeat the consonants initially spoken by the examiner. The participant was issued a point for each correct consonant given, totaling 15 points for each period (overall total of 45 points). There were no stopping rules for the CCC aside from full completion of the test with the participant attempting all levels of the test.

fNIRS and Hemodynamic Measures

A continuous wave two-channel dual wavelength (760 nm, 850 nm) fNIRS machine was used (Artinis Oxymon MK III, the Netherlands) to monitor hemodynamic measures (O_2Hb, HHb, HbDiff [O_2Hb minus HHb], and tHb) over the left and right PFC. The fNIRS optodes were precisely positioned over the forehead immediately above the supraorbital ridges on either side of the midline with the detector–emitter distance of 4.5 cm for each side to minimize signal contamination from extracerebral circulation.[30] This resulted in an approximate penetration depth of 2.7 cm (60% of 4.5 cm).[31] The midpoints of the detector–emitter distance corresponded to Fp1 and Fp2 in the International 10–20 system[32] which have been associated, in fMRI studies, with better neuroimaging signals in mental testing.[33,34] These locations have also been used with digit span and other cognitive testing.[22,23]

fNIRS sampling rate was at 10 Hz throughout testing, and participants wore a black blindfold to prevent distraction as well as to reduce ambient light. After sitting quietly

for 2 minutes to establish a baseline and regularize fNIRS signals, the participant was asked to repeat the vowels (a, e, i, o, and u) over 30 seconds as the control condition.[22]

After the initial baseline and control condition, testing continued as per the randomly ordered and counterbalanced digit span task and CCC. To minimize fatigue, a 2-minute period of quiet seated rest was inserted between each task. The participant was encouraged to restrict verbalizations to test responses only and also to minimize body movements during the entire test period.

Posttest Interview and Debriefing

On completion of the final memory test, the blindfold and optodes were removed and the participant asked to rate the strenuousness of the testing on a scale of 0–5 (0, no strain at all; 5, extremely strenuous).[35] The participant was also asked to list the strategies that he used during testing to aid performance. The posttest session was not included in the hemodynamic measures.

fNIRS Analysis

The hemodynamic changes were calculated by the manufacturer-supplied software using the modified Beer–Lambert Law.[36] A moving average of five samples per second was used to smooth the traces and facilitate analysis of the trends in the hemodynamic variables. Predetermined events were inserted in the fNIRS output to allow calculation of delta values. A colleague, unfamiliar with the study objectives, identified peak values in the fNIRS trace. The hemodynamic variables were monitored in real time and averaged over 5-second intervals using the data acquisition software (Artinis Medical Systems Inc, the Netherlands). Delta values were calculated (peak minus control) similar to the procedure of Kaneko et al[22] See Figure 1 for calculation of delta values in a representative trace of a normotensive participant.

To address concerns about the volume of the frontal sinuses and scalp to cortex distance biasing fNIRS hemodynamic scores,[37] we introduced head circumference as a covariate.

A laterality ratio score, previously used to assess prefrontal asymmetry during electroencephalogram (EEG) studies[38] and in fNIRS research,[26] was calculated using the following equation:

$$[\text{right} - \text{left side}] \times /[\text{right} + \text{left side}] \text{ for changes in } O_2Hb \text{ and tHb}$$

By convention, positive laterality ratio scores would indicate that larger increases in O_2Hb and tHb are occurring in the right side, whereas negative scores indicate larger changes are occurring in the left side.[26,38] To further clarify the differences between the groups on behavioral performance and hemodynamic changes, we reported efficiency measures for PFC hemodynamic changes. The efficiency

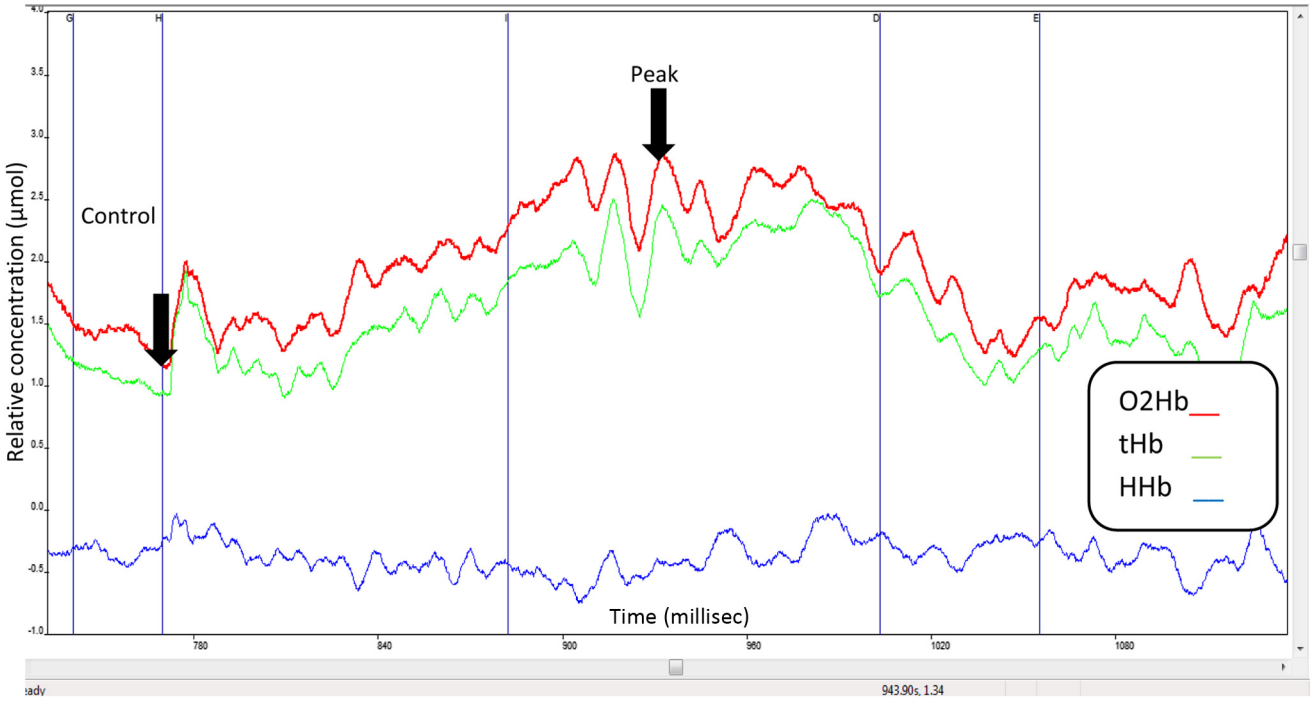


Figure 1. This outlines a representative trace of a normotensive participant identifying trends of O_2Hb, tHb, and HHb. Delta values are calculated as peak concentration in the respective trace minus the average concentration of the control condition. HHb, deoxyhemoglobin; O_2Hb, oxyhemoglobin; tHb, total hemoglobin.

measures were a modification of those suggested by Paas and Van Merriënboer[39] and calculated as follows:

$$\text{Hemodynamic Changes Efficiency} = \text{Cognitive Test scores}/O_2Hb,\ tHB,\ HbDiff$$

Statistical Analysis

Normality of the data was initially examined using the Shapiro–Wilks test. Independent *t* tests were used to identify differences between normotensive and hypertensive groups in the areas of age, body mass index, and years of education. Statistical analysis of all hemodynamic measures was performed using delta values which are consistent with methods used in continuous wave fNIRS measurements.[40] All comparisons were conducted after matching 15 normotensive participants with 15 hypertensives on age. A two-way repeated-measures analysis of covariance (ANCOVA) was used to identify differences in behavioral performance between the normotensive and hypertensive groups for the four cognitive performance tests.

Also, a three-way repeated-measures ANCOVA was used to investigate differences between normotensive and hypertensive participants on their PFC hemodynamic responses during testing. In these analyses, group (normotensive and hypertensive) was the between-subject factor and the four tests (DSF, DSB, DSS, and CCC) and side (left and right) were the within-subject factors. Mauchly test of sphericity was performed for the effect of test in the ANCOVA, and "F" ratios were adjusted using the Greenhouse–Geisser procedure. The Bonferroni correction for $P < .05$ was applied to control for type 1 error in the above ANCOVA analyses. Significant "F" ratios were analyzed using the Scheffé post hoc procedure.

Pearson product moment correlation coefficients were used to examine the relationship between the hemodynamic measures, behavioral test scores, and mental effort in each group during the tests. The Statistical Package Social Sciences SPSS (IBM version 21) was used for all statistical analyses (SPSS Inc, Chicago, USA).

Results

Sample Size and Participant Characteristics

The eventual sample was all nondepressed individuals consisting of 15 normotensive and 15 hypertensive males matched on age (Table 1). Seven of the hypertensives were on medically prescribed angiotensin receptor blockers, five on calcium channel blockers, whereas the others were on a combination of angiotensin-converting enzyme inhibitors and diuretics. The status of all the hypertensives was deemed "well controlled" by their family physician.

All participants were right hand dominant except for one in each group. They were fluent in the English language with English as the second language in half of the participants of each of the two test groups. All participants had resided in the Edmonton region in the province of Alberta, Canada, for at least 2 years immediately before testing. Both groups were composed of the diverse ethnic subpopulations that comprise the local community; namely, Afro-Canadian, Caucasian, Indo-Canadian, and Chinese-Canadian. Levels of education ranged from 13 to 21 years of formal education. Occupational categories based on skill type as per National Occupational Classification[41] showed a majority in the sedentary to light level category ("white-collar" jobs) for both groups with a single tradesperson in each group.

The procedure described by Keppel and Wickens[42] was used in interpreting the results of the ANCOVA. Head circumference as a covariate did not affect the significance of the results.

Comparison of Behavioral Performance

The hypertensive group demonstrated impaired behavioral performance on the four cognitive tests when compared with the normotensive group ($P = .027$; observed power = 0.613) as illustrated in Figure 2.

Within the CCC, there was a significant decrease in performance between the 9-second and 36-second delay periods in normotensive participants ($P = .014$) and for

Table 1
Characteristics of matched normotensive and hypertensive participants (mean ± SD)

Group	Age	Body Mass Index	Code for Physical Activity	Years of Formal Education	Resting Systolic BP	Resting Diastolic BP
Normo (N = 15)	38.47 ± 8.03	27.75 ± 3.38	4.64 ± 2.12	16.60 ± 2.64	117.08 ± 11.96	80.43 ± 7.24
Median	40	27.36	5.5	17	112	80
Hyper (N = 15)	42.20 ± 10.95	29.47 ± 4.56	4.67 ± 2.32	17.47 ± 2.59	130.54 ± 11.07*	86.17 ± 5.01†
Median	44	27.69	6.0	17	128	88

BP, blood pressure; Hyper, hypertensive; Normo, normotensive; SD, standard deviation.
Code for physical activity = 1 (least active)–7 (most active) (as per Ross and Jackson 1990).
* Significant at $P = .006$ (hypertensive with higher resting systolic blood pressure).
† Significant at $P = .03$ (hypertensive with higher resting diastolic blood pressure).

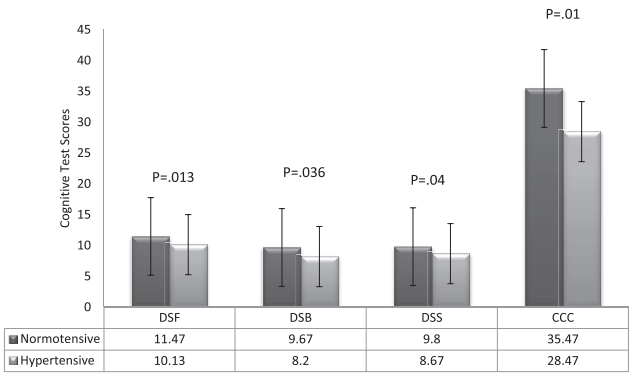


Figure 2. The behavioral performance scores are illustrated for normotensive and hypertensive participants on the four cognitive tests. Hypertensive participants' performance was significantly lower on these tests. CCC, auditory consonant trigrams; DSB, digit span backward; DSF, digit span forward; DSS, digit span sequencing.

hypertensives ($P = .026$). An additional test of perceived mental effort identified a consistent but nonsignificant trend of higher mental effort in the hypertensive group.

Hemodynamic Changes During Cognitive Tests in Normotensive and Hypertensive Groups

A representative trend of the hemodynamic responses during the four cognitive tests is illustrated in Figure 1. In both groups of participants, these trends were similar, but the magnitude of these changes was different across the groups. One should caution that comparing traces across groups might not be accurate in fNIRS analysis.[19] At the start of the test, O_2Hb, tHb, and HbDiff demonstrated systematic increases with a concomitant decrease in HHb. On termination of the test, these variables reverted toward baseline; a similar response was demonstrated with each subsequent test.

Mean O_2Hb values noted for the hypertensive group were uniformly higher across the left and right PFC but was not significantly different from the normotensives ($P = .201$; observed power = 0.244). In pairwise comparison of the tests across both groups, there was a significantly higher mean O_2Hb for CCC ($P < .001$; observed power = 0.998) in the left and right PFC.

Similarly, the overall trend was for higher tHb concentration in the left and right PFC in the hypertensive group compared with normotensives, but this also did not reach significance ($P = .239$; observed power = 0.213). On the main effect of side, there was no significant difference between the left and right PFC on the tHb and O_2Hb variables. However, descriptive plots of the variable means revealed a distinctly sharper increase in O_2Hb and tHb concentrations in the left side of the hypertensives.

HbDiff revealed a nonsignificant difference between the groups with higher changes noted in the hypertensive group (mean ± standard deviation 4.487 ± .63; 4.870 ± .63). Similar to O_2Hb and tHb, the plot of HbDiff changes revealed a distinct trend for sharper rise in concentration changes in the left side of the hypertensive group. In pairwise comparisons of the tests on the variable HbDiff, CCC resulted in significantly greater changes than the other three tests ($P < .001$).

A descriptive charting of the calculated performance efficiency scores for O_2Hb, tHb, and HbDiff across the groups demonstrated a consistent trend of lower efficiency in the hypertensive group. Figure 3 (panels A, B, and C) illustrates this pattern.

Laterality Testing and Correlations Between Cognitive Tests and Hemodynamic Changes

A trend for negative laterality scores is suggestive of greater left PFC changes.[26] Laterality scores for O_2Hb and tHb changes were not significant across the groups; however, in the hypertensive group, three of the four tests resulted in negative laterality scores. In the hypertensive group, the largest changes were in the left side for O_2Hb, tHb, and HbDiff variables.

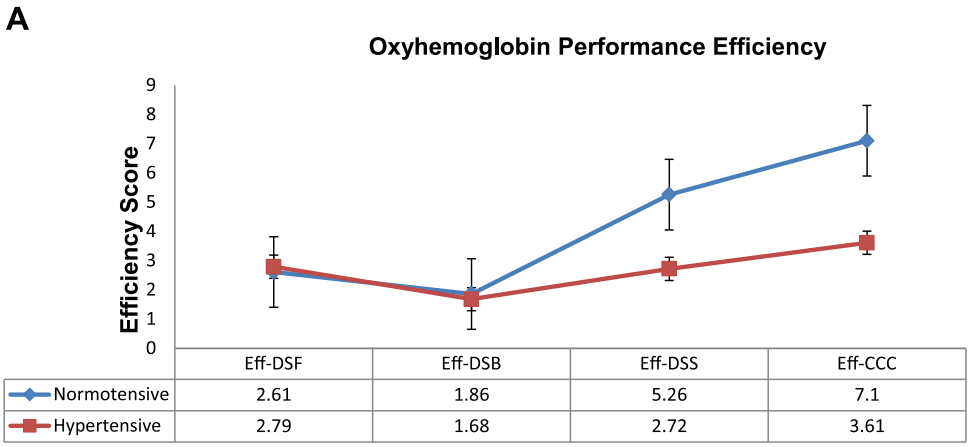
There were no significant correlations in the normotensive group between behavioral performance and O_2Hb and tHb changes in the right and left PFC (correlations ranged from −0.143 to −0.23). However, in the hypertensive group, significant correlations were observed between: (1) tHb in the left and right PFC during DSB and (2) O_2Hb in both the left and right PFC during DSB. Additionally, Figure 4A illustrates the trend between oxygenation and mental strain across both groups indicating statistical significance for the left and right PFC in the hypertensives during DSF ($P < .05$). Figure 4B illustrates the comparison of performance and subjective mental strain across the groups.

Discussion

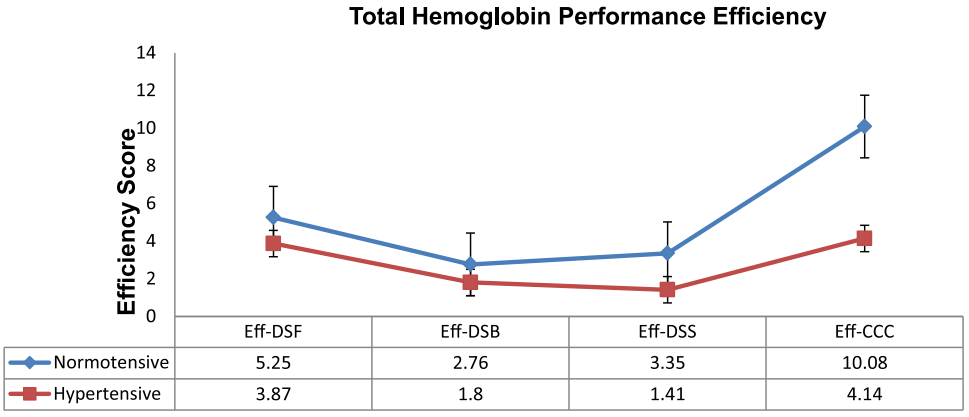
Modifications in cerebrovascular reserve as a consequence of small vessel disease in hypertension can be viewed through the interplay between behavioral performance, hemodynamic changes, and the performance efficiency of PFC function in general. These modifications will be compared with normotensives and discussed in the following paragraphs from the following perspectives: (1) comparison of cognitive performance, (2) comparison of hemodynamic responses, (3) mental effort and cognitive adjustment, (4) PFC lateralization and functional compensation, and (5) relationship between behavioral performance and hemodynamic responses in the groups.

Comparison of Cognitive Performance Between Normotensive and Hypertensive Participants

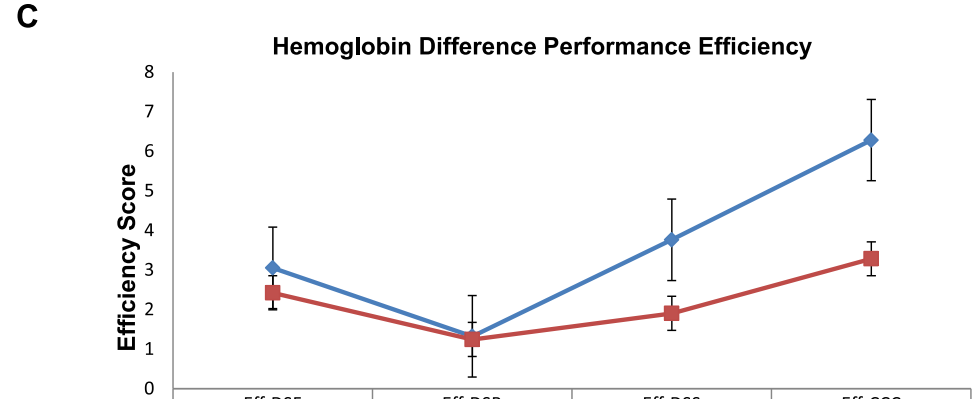
Our first postulate that there would be a significantly impaired behavioral performance by the hypertensive group



	Eff-DSF	Eff-DSB	Eff-DSS	Eff-CCC
Normotensive	2.61	1.86	5.26	7.1
Hypertensive	2.79	1.68	2.72	3.61



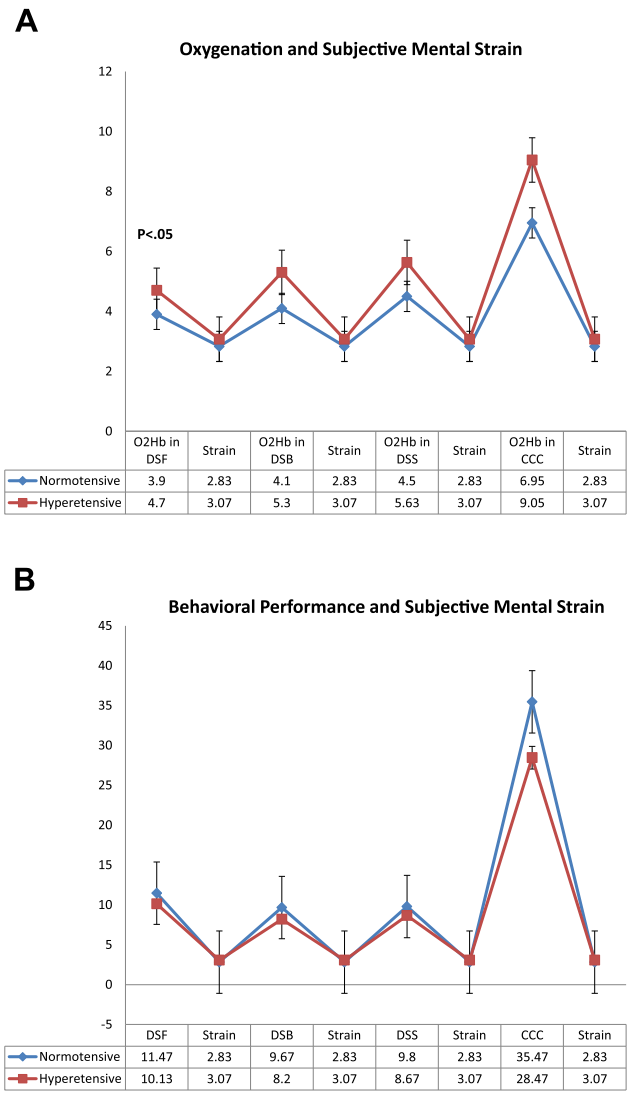
	Eff-DSF	Eff-DSB	Eff-DSS	Eff-CCC
Normotensive	5.25	2.76	3.35	10.08
Hypertensive	3.87	1.8	1.41	4.14



	Eff-DSF	Eff-DSB	Eff-DSS	Eff-CCC
Normotensive	3.05	1.32	3.76	6.28
Hypertensive	2.42	1.24	1.9	3.28

Figure 3. (A–C) Efficiency scores were calculated with hemodynamic changes (O_2Hb, tHb, and HbDiff) as a function of behavioral performance on the cognitive tests. Higher efficiency scores are noted in the normotensive. Eff_CCC, efficiency score for auditory consonant trigrams; Eff_DSB, efficiency score for digit span backward; Eff_DSF, efficiency score for digit span forward; Eff_DSS, efficiency score for digit span sequencing; O_2Hb, oxyhemoglobin; tHb, total hemoglobin.

was supported. Additionally, a description of performance efficiency scores (O_2Hb, tHb, and HbDiff) showed a trend of diminishing performance efficiency in the hypertensives (Figure 3: panels A, B, and C). To our knowledge, this study is the first to demonstrate a pattern of impaired cognitive performance in conjunction with trends of lowered hemodynamic efficiency in a hypertensive group. Importantly, our study participants (19–55 years) were still within their



	O2Hb in DSF	Strain	O2Hb in DSB	Strain	O2Hb in DSS	Strain	O2Hb in CCC	Strain
Normotensive	3.9	2.83	4.1	2.83	4.5	2.83	6.95	2.83
Hyperetensive	4.7	3.07	5.3	3.07	5.63	3.07	9.05	3.07

	DSF	Strain	DSB	Strain	DSS	Strain	CCC	Strain
Normotensive	11.47	2.83	9.67	2.83	9.8	2.83	35.47	2.83
Hyperetensive	10.13	3.07	8.2	3.07	8.67	3.07	28.47	3.07

Figure 4. (A) This illustrates the comparison between normotensive and hypertensive participants in reported mental effort and oxygenation (O_2Hb) changes during the four cognitive tests. Mental effort was on a five-point rating scale with 5 indicating greatest subjective mental effort and 0 indicating no effort at all. (B) This is an illustration of the comparison between normotensive and hypertensive participants on behavioral performance and mental effort during the four cognitive tests. Performance is rated as per test manual, whereas mental effort was on a five-point rating scale with five indicating greatest subjective mental effort and 0 indicating no effort at all. CCC, auditory consonant trigrams; DSB, digit span backward; DSF, digit span forward; DSS, digit span sequencing; O_2Hb, oxyhemoglobin.

most occupationally productive years. This finding provides relevant information on the potential impact of the disease on human productivity. Previous studies that identify cognitive impairment in hypertensives have mostly focused on elderly and less active populations which necessarily provoke questions about ‘‘normal’’ aging and deconditioning as confounding variables.[43] Our findings allow the debate on the hypertension–cognition relationship to surpass these basic queries and initiate questions on underlying mechanisms. Hemodynamic changes in the PFC are likely part of the neural mechanism mediating cognitive performance in the disease.

Comparison of Hemodynamic Responses Between Normotensive and Hypertensive Participants

As a second hypothesis, we postulated higher O_2Hb and tHb changes in the hypertensives as a feature of PFC inefficiency associated with the disease, that is, increase hemodynamic changes despite impaired performance. There was a trend for higher mean concentrations for both O_2Hb and tHb. Although the difference was not statistically significant, this nonsignificance may be the result of low statistical power. Increase in O_2Hb during all the tests was accompanied by a trend of decreasing or unchanged HHb (Figure 1), consistent with what is considered a typical pattern of neuronal activation in the PFC.[18] We can thus infer that the hypertensive group was demonstrating increased neuronal activation in the PFC despite a relatively impaired behavioral performance. Increases in neuronal activation on cognitive tasks in healthy and diseased populations have been previously observed in fNIRS activation studies,[44] as well as similar fMRI[45] and PET studies.[46] In this study, however, the higher O_2Hb levels for the hypertensive group suggest the possibility of a higher neuronal activation rate when compared with normotensives. A concurrent trend for higher HbDiff suggests attempts at greater PFC oxygen extraction and workload[47,48] in the hypertensive group. Léon-Carrion et al,[49] reporting on healthy participants, stated that cognitive performance levels tended to parallel O_2Hb levels in the PFC. Results of our study, in addition to being consistent with these findings, also demonstrated an important comparative difference between a relatively young hypertensive group and normotensives. The nonsignificant trends of higher O_2Hb, tHb, and HbDiff levels in the hypertensive group despite a statistically significantly impaired behavioral performance suggest diminished cognitive work efficiency. This parallels the trends in hemodynamic efficiency measures previously mentioned. Concurrent with performance efficiency, subjective mental effort is an important variable for consideration.

Mental Effort and Cognitive Adjustment

In the posttest interview, the hypertensives reported higher overall subjective mental strain during cognitive testing. With the significantly impaired performance accompanying the pattern of higher strain and oxygenation levels in the hypertensives, it would appear that this group

was striving for efficiency. The Compensation-Related Utilization of Neural Circuits Hypothesis indicates that given similar memory loads, individuals with poorer memory capacities tend to deploy more brain activation than those with higher abilities.[50] In this study, the trend for higher hemodynamic changes (O_2Hb, tHb, and HbDiff) in the hypertensive group, coupled with objectively poorer performance, appears to support Compensation-Related Utilization of Neural Circuits Hypothesis. The subjective reports of increased mental strain represent increased effort associated with testing. It is a reasonable suggestion that this scenario is attributable to a decreased memory span, accompanying the physiological effects of hypertension.

Nyberg et al[51] demonstrated that a vital determinant of working memory span is the ability to adequately engage the frontal lobe while attending to the demands of a particular task. According to these researchers, this signifies the importance of ''relative task difficulty'' or the demanding nature of the memory task. The hypertensives in our study might be engaging the PFC more intensely in an effort to compensate for a ''relatively'' more difficult task than that experienced by the normotensive, albeit for the same test. O_2Hb changes that vary with mental strain may provide a neurovascular index for the reported mental effort. To further explain performance and possible compensatory mechanisms accompanying hypertension, interhemispheric adjustments in brain oxygenation provide a fertile area of inquiry.

PFC Lateralization and Functional Compensation

Our third hypothesis that there would be significant changes in asymmetry in the right and left side oxygenation and blood volume was not supported statistically. However, there was a distinct trend of increasing blood volume changes in the left side of the hypertensive group. This may provide a broader theoretical explanation of the possibility of compensatory effects of hypertension during cognitive testing.

There are known trends in neuronal compensation across the hemispheres to address performance deficits at the individual level.[30,52] Hence, comparing hemodynamic changes in the left and right PFC during cognitive testing of hypertensives may inform on a similar compensatory phenomenon. The laterality ratio scores designed to measure asymmetry in PFC activation patterns indicated that during the four tests, the hypertensives had negative laterality scores for tHb. This suggests by convention that increases in the left PFC blood volume changes were trending larger than the right during testing.[26] Furthermore, the three variables O_2Hb, tHb, and HbDiff all showed a trend of sharper increases in the left PFC of the hypertensives. Given the behavioral performance differences between the groups previously mentioned, it is possible that the left PFC became increasingly activated, additive to the right PFC, in an attempt to compensate for deficiency in performance. A similar compensatory phenomenon has been reported in aging studies.[30,50] The relationship between behavioral performance and hemodynamic responses may further inform on the possibility of compensation across the hemispheres in this disease.

Relationship Between Behavioral Performance and Hemodynamic Responses in Normotensive and Hypertensive Participants

Our fourth hypothesis proposed a significant correlation between O_2Hb and tHb changes and behavioral performance in the groups. Significant correlations on these two variables were identified only in the hypertensive group. They occurred between these measures and DSB on both the left and right PFC. Interestingly, Kaneko et al[22] reported that DSB in a healthy population resulted in greater levels of PFC activation than the DSF. Given the striving for efficiency in the hypertensive group previously discussed, it is possible that higher activity during DSB testing resulted in a greater drive to compensate for behavioral deficiency in the hypertensive. This could have resulted in the significant correlation between performance and hemodynamic responses, as well as the increased activity in the left PFC. One should also note that of the four tests performed in our study, hypertensives underperformed on the DSB.

Hoshi et al[23] reported that DSFs resulted in increased activation in the right PFC in healthy participants. Although no previous information exists for CCC or for hypertensives in this regard, our findings indicate that the pooled tests, digit span, and CCC, trended toward more pronounced left PFC activation. The possibility exists that these changes are the result of microvascular pathology typical of hypertensive disease and are reminiscent of compensatory age-related changes. This assertion should be tempered with knowledge of the limitations of our experimental procedure.

Limitations of the Study

In this study, there was an issue of statistical power due to small sample size. The effect of varied hypertension medication use on brain function is not well explained in the literature and is likely to impact the results. Furthermore, the methodological restrictions of administering the digit span task and CCC with unique rules of test administration made testing cumbersome. Additionally, the use of fNIRS for hemodynamic evaluation with this particular test combination is unusual. However, in future analysis, an alternative method using a better level of discrimination on cortical activation such as the ''slope method'' as advocated by Mandrick et al[53] would be appropriate.

Continuous wave fNIRS, as used in this study, applies continuous near infrared light and measures the attenuation of the incident light to quantify concentration changes in hemoglobin. When hemodynamic concentration changes are

localized, as in brain activation studies, the light differential path length factor through the tissues is assumed to be constant and this is likely to be inaccurate.[19,40] Hence, delta values, not absolute concentrations, are used in calculating hemodynamic changes with brain activation. This limits how the results can be generalized and used clinically.

Another limitation in fNIRS measurement of the brain is in accounting for the scalp to cortex distance. The variation in size of the frontal sinuses and scalp thickness affects light penetration of the PFC and thus fNIRS recording. Given that the same emitter–detector distance was used in all cases, the degree of activated cortex measured would vary given individual differences in frontal sinus parameters.[37] Additionally, continuous wave fNIRS has shown that even under resting conditions, hemoglobin oxygenation fluctuates.[54] Systemic fluctuations such as arterial pulse oscillations and respiration result in fluctuating patterns of oxygenation. Furthermore, slower vasomotor oscillations from the pial arteries[31] were not accounted for in this study.

Although the four cognitive tests were counterbalanced, the control condition was administered at the beginning of testing. This could have a variable effect on calculated delta values for each test.

The volunteers in this study were characteristically of a higher educational level and mostly used in white-collar occupations. Hence, the findings would be limited in transfer to other groups. Furthermore, the time since diagnosis of hypertension ranged from 1 to 20 years. The small vessel disease and perfusion changes in the PFC would be quite variable in our sample. Inclusion of ischemic scores such as the Hachinski Ischemic Index[55] would render the results more clinically pertinent to the implications of small vessel disease in hypertension.

Conclusions

Cerebrovascular vasodilatory reserve correlates with the physiological markers of hypertension such as endothelial dysfunction in brain microvasculature. Brain vascular reserve is likely to influence behavioral performance and individual functional capacity demonstrable on memory tasks. Oxygenation and blood flow changes help to identify the efficiency of neurovascular coupling in the brain that supports this reserve. Efficiency or lack thereof in the features of cerebral neurovascular coupling is ultimately revealed in behavioral performance and hemodynamic adjustments accompanying the reduced cognitive function.

The alteration in cognitive performance as demonstrated in this study in a relatively young group of essential hypertensive males advocates the importance of addressing the disease through a prism of functional capability. The possible attempts at physiological compensation in the PFC propose a premature aging inclination. Such a feature, combined with impaired performance, should it be confirmed, is not unique in organ systems affected by hypertension. However, these findings and their potential impact on the executive function in the prime years of productive life focus clinical attention on important parameters of the disease well in advance of old age.

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