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Neurocognitive Function in Children with Primary Hypertension after Initiation of Antihypertensive Therapy

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Abstract

Objective—To determine the change in neurocognitive test performance in children with primary hypertension after initiation of antihypertensive therapy.

Study design—Subjects with hypertension and normotensive control subjects had neurocognitive testing at baseline and again after 1-year, during which time the subjects with hypertension received antihypertensive therapy. Subjects completed tests of general intelligence, attention, memory, executive function, and processing speed, and parents completed rating scales of executive function.

Results—Fifty-five subjects with hypertension and 66 normotensive control subjects underwent both baseline and 1-year assessments. Overall, the BP of subjects with hypertension improved (24-hour systolic BP load: mean baseline versus 1-year, 58% versus 38%, $P < .001$). Primary

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multivariable analyses showed that the hypertension group improved in scores of subtests of the Rey Auditory Verbal Learning Test (RAVLT), Grooved Pegboard, and Delis-Kaplan Executive Function System Tower Test ($p < .05$). However, the control group also improved in the same measures with similar effects sizes. Secondary analyses by effectiveness of antihypertensive therapy showed that subjects with persistent ambulatory hypertension at 1-year (n = 17) did not improve in subtests of RAVLT and had limited improvement in Grooved Pegboard.

Conclusions—Overall, children with hypertension did not improve in neurocognitive test performance after 1 year of antihypertensive therapy, beyond that also seen in normotensive controls, suggesting improvements with age or practice effects due to repeated neurocognitive testing. However, the degree to which antihypertensive therapy improves BP may affect its impact upon neurocognitive function. .

Keywords

neuropsychological testing; blood pressure; obesity; treatment

Young adults with hypertension have lower performance on neurocognitive testing compared with matched normotensive control subjects, a finding postulated to represent an early manifestation of hypertensive target organ damage to the brain.(1, 2) Furthermore, hypertension in both adolescence and young adulthood has been associated with decreased neurocognitive test performance in mid-life, raising concern for a link between early hypertension and subsequent cognitive decline later in life.(3–5) Despite these observations, results of studies of the impact of hypertension treatment in adults on subsequent neurocognitive test performance have been mostly inconsistent and inconclusive.(6) As a consequence, a recent scientific statement from the American Heart Association on the impact of hypertension on cognitive function identified as a critical question whether treatment as early in life as possible, such as treatment in adolescence, would offer advantages for subsequent cognitive function.(7)

Studies focusing on the impact of childhood primary hypertension during youth itself have found that children with hypertension often demonstrate similar target organ damage findings as do adults, particularly left ventricular hypertrophy and increased carotid intima-media thickness.(8, 9) However, there have been only limited assessments of hypertensive target organ effects on the brains of children. We established a prospective, multicenter study of neurocognition in children with primary hypertension.(10) Our specific aims were to compare the performance on neurocognitive testing of newly diagnosed subjects with untreated hypertension with that of the performance of matched normotensive controls at baseline and to evaluate the effect of 1-year of antihypertensive therapy on neurocognitive test performance. We recently reported results of the baseline comparison, showing that children with hypertension had worse performance on neurocognitive testing compared with that of the normotensive control subjects, particularly in the domains of attention, learning, and memory.(11) Here, we report the results of the effect of 1-year of antihypertensive therapy on neurocognitive test performance in the same cohort. We hypothesized that children with primary hypertension would show improvement in neurocognitive test performance after antihypertensive therapy; whereas the neurocognitive test performance of the normotensive control subjects would remain unchanged over the same time period.

Methods

The participants in this study were the subjects with hypertension and control subjects from our initial report who subsequently returned for reassessment after 12 months. During the 1-year interval between study visits, the subjects with hypertension received standard of care antihypertensive therapy as detailed below. Control subjects were not seen between the initial assessment and the 1-year visit. Hypertension and control subjects completed the same neurocognitive assessment at baseline and again at 1- year. The study methods have been previously described in detail.(10)

Participating recruitment sites included the University of Rochester, Emory University, Maimonides Medical Center, and the McGovern Medical School at UTHealth. Newly diagnosed children ages 10–18 years with untreated hypertension were enrolled through the Pediatric Hypertension Clinics at each site. For comparison, normotensive, healthy 10- to 18-year-old children were enrolled from participating general pediatrics and family medicine primary care practices. Our initial report compared 75 hypertension and 75 control subjects who were frequency matched for sex, proportion with obesity [body mass index (BMI) ≥95th percentile], and maternal education. Race and ethnicity were not formally matched, but the results were adjusted for these characteristics in the multivariate analyses. At baseline, each subject with hypertension had a history of office hypertension that was confirmed with 24-hour ambulatory blood pressure monitoring (ABPM) by the presence of mean systolic and/or diastolic awake blood pressure (BP), mean sleep BP, or both ≥95th percentile.(12) Hypertension subjects were also included if the mean ambulatory BP was <95th percentile, but the subject had both BP load >25% (ambulatory prehypertension) and left ventricular hypertrophy (LVH) on echocardiogram. Only 3 hypertension subjects were included by these alternate criteria; therefore, their results were combined with the other hypertension subjects in the current analysis. Normotensive control subjects were required to have office normotension, confirmed by mean awake and sleep SBP and DBP <95th percentile and 24-hour SBP and DBP load <25% on ABPM.(12) Both hypertension and control subjects underwent repeat ABPM at the 1-year visit to assess the adequacy of the hypertension treatment in the hypertension subjects and to confirm the persistence of normotension in the control subjects. All subjects with hypertension underwent a complete 2-dimensional echocardiogram at the baseline visit that was read centrally at the University of Rochester. Left ventricular hypertrophy was defined as a left ventricular mass index ≥95th percentile. (13) Echocardiogram and ABPM procedures have been described in our earlier report.(11) All subjects had baseline central laboratory evaluations, including fasting lipid profile, insulin level, glucose, and C- reactive protein (CRP). Homeostatic model assessment (HOMA) for insulin resistance was calculated as glucose x insulin/405.

Exclusion criteria were as follows: being on medication for attention deficit/hyperactivity disorder (ADHD), having a pre-existing learning problem/disability (defined as having an Individual Educational Plan or Section 504 Plan at school), any disorder of cognitive impairment, history of chelation treatment for elevated lead level, history of chronic disease (known renal, cardiovascular, gastrointestinal tract, hepatic, endocrine, or rheumatologic disease), pregnancy or breastfeeding, previous sleep study diagnosis of obstructive sleep apnea, a diagnosis of secondary hypertension, and previous or current treatment with

antihypertensive medication. The study was approved by the institutional review board at each site, and parental permission was obtained (as well as subject assent when age-appropriate).

Hypertension and control subjects underwent the same neurocognitive assessment at baseline and at the 1-year follow-up visit, a study design that allowed the assessment of change in test performance in the hypertensive subjects after one year of antihypertensive therapy. The neurocognitive assessment in the control subjects was repeated at 1-year in order to detect any improvement in test performance due to increasing age or due to the practice effect, the propensity for scores to improve by virtue of learned strategies or recall of task content from repeated test administration.(14) As previously described, the neurocognitive assessment included both laboratory performance-based measures and behavior rating scales.(10) The laboratory tests included measures of executive function (measures of problem solving/planning, set-shifting, response inhibition, vigilance, and working memory), verbal learning and memory, attention, fine-motor dexterity, and general intellectual functioning. Behavior ratings of executive function included the Behavior Rating Inventory of Executive Function (BRIEF), completed by the parent. Table I lists the neurocognitive measures, along with the primary subtests for each test and the cognitive domain assessed. Mood symptoms were also evaluated with the child self- report measures of the Multidimensional Anxiety Scale for Children (MASC) and the Child Depression Inventory (CDI). Lastly, parents completed the Sleep-Related Breathing Disorder Scale of the Pediatric Sleep Questionnaire (PSQ-SRBD) as an estimate of disordered sleep, a common comorbidity in obese children and a potential confounder of neurocognitive test performance.(15, 16)

This study was not a clinical trial, but instead an observational study of neurocognitive changes that occur during usual standard of care. We did not randomize subjects to different treatments. Instead the hypertension subjects were treated according to local standards and national consensus guidelines as decided by the treating physician,(17) with some standardization across sites as detailed below. The control subjects were normotensive children who did not receive any treatment. Antihypertensive treatment began only after completion of the baseline neurocognitive assessment. All hypertension subjects met with a nutritionist at the beginning of the study and again at 3 - 6 months to receive exercise counseling and to review the Dietary Approaches to Stop Hypertension (DASH) diet, salt restriction, and if needed, weight loss counseling.(17) Antihypertensive medication was initiated at the discretion of the site physician with the following standardizations: For hypertension subjects with stage 1 hypertension without LVH, antihypertensive medication was considered after three months if there was no indication of improvement with lifestyle modification. Antihypertensive medication could be started sooner in subjects who had already failed a concerted effort at lifestyle modification in the judgment of the site physician. In accordance with consensus guidelines, subjects with stage 2 hypertension and/or LVH were started on antihypertensive medication from the outset. When antihypertensive medication was indicated, the initial drug was lisinopril, as angiotensin converting enzyme (ACE) inhibitors are the most common class of antihypertensive medication prescribed by pediatric nephrologists for the treatment of primary hypertension.(18) Female subjects of child bearing potential and their parents were counseled on the

potential teratogenic risks of ACE inhibitors, and urine pregnancy tests were performed prior to initiating ACE inhibitor therapy, and then every 3 months for the duration of the study. Blood chemistry measures for potassium and creatinine were performed within 4 to 6 weeks of starting lisinopril. Thiazide diuretics or calcium channel blockers were used as second-line agents if needed. Amlodipine was recommended as an alternate choice for subjects who did not tolerate lisinopril as the first-line treatment. Clonidine and beta blockers were avoided.

Once antihypertensive medication was initiated, subjects were seen every 4 to 6 weeks in the site's Pediatric Hypertension Clinic to have their therapy titrated until adequate control of hypertension was achieved, defined as manual office BP < 95th percentile.(17) Initial dosing of antihypertensive medication and subsequent dose adjustments were at the discretion of the site physician. Once adequate control was achieved, the hypertension subjects were followed every 3 months to monitor BP control and adjust antihypertensive therapy accordingly. The number of visits with adequate control before extending the visit interval to every 3 months was at the discretion of the site physician. If a medication increase was needed, the subject was seen again every 4 to 6 weeks until BP control was re-established. Subjects achieving BP control with lifestyle modification alone were seen in the Pediatric Hypertension Clinic every 3 months throughout the course of the study. Upon enrollment, the subjects were given a home digital BP monitor (OMRON BP760) to measure their home BP once daily in the week prior to their next visit. The subjects kept a log of these measurements and they were asked to bring the log to all visits to help determine the response to therapy and to determine the presence of a white-coat effect at the visit. At both the baseline and 1-year neurocognitive assessment, BP was measured three times at 5 minute intervals by an automated oscillometric device at the site Clinical Research Center, and the BP for that study visit was calculated as the average of the 2nd and 3rd reading.

In order to encourage compliance, the hypertension subjects on antihypertensive medication were contacted at least monthly by the site study coordinator to remind the subject to take his/her medication. Hypertension subjects managed with lifestyle modification alone were not contacted monthly. Coordinators also reminded all subjects of their upcoming interim visit a week prior to the scheduled appointment. When a hypertension subject missed an interim visit, they were contacted within a week by the study coordinator and rescheduled for as soon as possible. Subjects with multiple consecutive missed interim visits were repeatedly rescheduled until the site physician felt that further efforts were futile and that the subject was lost to follow-up. Control subjects were contacted every 3 months to update their contact information.

Statistical Analyses

Demographics and baseline outcomes were compared between hypertensive and control groups using t-tests or Chi-square tests when appropriate. For the primary analyses, the changes in neurocognitive test scores from baseline to 1-year were compared between the hypertension and control groups using analysis of covariance (ANCOVA) models with the study group as an independent variable after adjusting for corresponding baseline of the neurocognitive test score, age, sex, PSQ-SRBD score, maternal education (< high school,

high school, college, > college), household income (<$25,000, $25,000–75,000, >$75,000), African-American race, baseline body mass index (BMI) z-score, change in BMI z-score from baseline to 1-year, and baseline HOMA value. Least Square Means (LSM) for within group effect, along with the between group treatment differences, and associated p-values were calculated. All tests of treatment effects were conducted as a two-sided alpha level of 0.05. Effect sizes (ES) were calculated by dividing the study group differences in the LSM changes by the pooled standard deviation of the changes. We did not adjust for testing of multiple hypotheses in the analyses. Patient baseline characteristics were compared between those subjects who remained and those subjects who were lost to follow-up. To ensure that the assumption of data missing completely at random for the primary analyses did not bias the results, we also carried out a version of the analyses after multiple imputation procedures for missing data using a multiple imputation algorithm based on multiple regression models. Using this imputation regression model, a missing value for a subject was imputed as a draw from the predictive distribution given the subject's baseline values and characteristics. This process was repeated five times and the results were combined into one multiple imputation inference.(19, 20)

Because a subset of the hypertension subjects still had BP in the ambulatory hypertension range at the 1-year assessment, we performed a secondary analysis by effectiveness of antihypertensive therapy with three groups: hypertension improved (HTN-I), hypertension not improved (HTN-NI), and controls with sustained normotension (Con-S). ANCOVA models were used to fit the data similarly as the primary analysis. All statistical analyses were conducted using SAS Version 9.4 (SAS Institute Inc, Cary, North Carolina.).

Results

Of 150 subjects, who were enrolled initially 121 (81%) provided baseline data returned for the 1-year visit, including 55 (73%) of the 75 subjects with hypertension and 66 (88%) of the 75 control subjects ($p = 0.04$). The subjects who returned were similar to the subjects who did not return in age, sex, race, ethnicity, maternal education, household income, WASI full scale IQ, CDI and MASC scores, and the baseline parent BRIEF MI summary score (data not shown). However, subjects who did not return had higher (worse) mean score on the baseline parent BRIEF BRI summary score compared with subjects who did return (T-score, 54.5 vs 46.6, $p < 0.001$). Among subjects who did not return, a higher proportion had BRI scores in the clinically significant range for executive dysfunction [BRI T-score ≥65; 6 of 29 (21%) vs 5 of 121 (4%), $p = 0.007$). Of the 6 subjects who did not return and who had BRI scores in the clinically significant range, 5 were from the hypertension subject group.

The 55 subjects with hypertension and 66 control subjects with both baseline and 1- year follow-up data were similar in age, sex, race, ethnicity, laboratory evaluation, and maternal education, but differed in household income. By definition, the hypertensive and control groups differed in baseline BP (Table 2; available at www.jpeds.com).

Anti-Hypertensive Treatment

Of the 55 subjects with hypertension, 11 were treated with lifestyle modification counseling alone and 44 were treated with lifestyle modification counseling and lisinopril. Three

patients required the addition of a second antihypertensive medication, 2 with chlorthalidone and 1 with amlodipine. Two patients were switched from lisinopril to losartan for complaints of cough and headache, respectively. One patient developed increased creatinine on lisinopril and was switched to amlodipine.

Comparison of ABPM measures at baseline and at 1-year confirmed that the hypertension subjects had lower BP after 1-year of antihypertensive therapy. Control subject blood pressure remained similar over the year in most ABPM measures, but increased by nighttime SBP index and 24hr SBP load. Body mass index (BMI) z-score did not change among hypertensive subjects, whereas there was a trend toward decrease in BMI z-score in the control subjects (Table 3). Further analysis of ABPM measures showed that of the 55 hypertensive subjects, 38 (69%) had successful treatment of their hypertension defined as ambulatory systolic and diastolic BP index <1.0 for both awake and sleep periods (24hr SBP load, baseline vs 1-year, 58.6% vs 24.5%, $p < 0.001$). By contrast, 17 (31%) of the hypertensive subjects still had persistent ambulatory hypertension at the 1-year assessment, defined as systolic and/or diastolic BP index ≥1.0 for either the awake or sleep period or both (24hr SBP load, baseline vs 1-year, 55.4% vs 69.5%, $p = 0.005$; Table 4 [available at www.jpeds.com]). The subjects with successful treatment did not differ significantly from those with persistent ambulatory hypertension in age, baseline BMI z-score, sex, maternal education, household income, race, or ethnicity (data not shown). Of the 17 subjects with persistent ambulatory hypertension, 4 (24%) had elevated office systolic and/or diastolic BP at the 1-year assessment, but 13 (76%) had normal office BP, consistent with ambulatory masked hypertension. Of the 38 hypertension subjects with successful treatment of their hypertension, 33 (87%) received antihypertensive medication compared with 9 (53%) of 17 hypertension subjects with persistent ambulatory hypertension ($p = 0.08$). Of the 66 control subjects, 56 had sustained ambulatory normotension at the 1-year assessment, but 10 had developed elevated ambulatory BP.

Neurocognitive Test Results

Primary Analyses—Within-group changes from baseline to 1-year with effect sizes are listed in Table 5 for both the hypertension and control groups. Comparisons of the between group changes are also shown to evaluate whether any improvement in the hypertension group was larger than that which may have also occurred in the control group. The hypertension group improved in scores of subtests of the RAVLT (verbal learning and memory), Grooved Pegboard (manual dexterity), and DKEFS Tower Test (executive function) with moderate effect sizes. However, the control group also improved in the same measures with similar effects sizes. There was no statistical difference in the change in scores between groups for these measures. The control group improved in scores for WISC-IV Spatial Span Forward (visual attention and memory) with a moderate effect size, whereas the hypertension group did not, and the between group comparison showed that the change in scores for the control and hypertension groups for this measure were significantly different. There were several other subtests where either the hypertension or the control group had statistically different within-group change in scores with small effect sizes, but where the difference in change between groups was not statistically different. Repeat

analyses after multiple imputation procedures to account for missing data did not show significantly different results from the primary analyses (data not shown).

Secondary Analyses—Table 6 shows neurocognitive test results according to effectiveness of treatment. For these analyses, there were three groups: 1) Hypertension subjects whose BP improved by ABPM (HTN-I, N = 38), 2) Hypertension subjects whose BP did not improve by ABPM (HTN-NI, N = 17), and 3) Control subjects who sustained normotension by ABPM (Con-S, N = 56). The group of control subjects who developed elevated BP (N = 10) was felt to be too small for secondary analysis of the neurocognitive data. Similar to results in the primary analyses, on multivariable analyses, HTN-I subjects and Con-S subjects showed significant within-group improvement in subtests of the RAVLT, with moderate effect sizes. In contrast, the HTN-NI group scored worse on the RAVLT List A Trial 1 and RAVLT List A Total subtests at 1-year compared with baseline, and the between-group difference was statistically significant between the HTN-NI group and both the HTN-I and the Con-S groups. HTN-NI group did show a slight improvement in RAVLT Short Delay Recall, but the effect size was small (ES = 0.12) compared with a moderate effect size for HTN-I (ES = 0.5) and Con-S (ES = 0.41). Also similar to results in the primary analyses, the HTN-I and Con-S groups showed within-group improvement in Grooved Pegboard with large effect sizes for both dominant hand (ES, HTN-I = 0.78; Con-S = 0.70) and non-dominant hand (ES, HTN-I = 0.61; Con-S = 0.69). In comparison, the HTN-NI group had only minimal improvement with only small effect sizes (ES, dominant hand = 0.27, non-dominant hand = 0.14),.

Likewise similar to results in the primary analyses, all groups improved in DKEFS Tower with similar effect sizes, and the Con-S group improved in Spatial Span Forward whereas the hypertension groups did not. The Con-S and HTN-I groups scored worse on CPT-II Variability, but all groups performed similarly in the other CPT-II subtests.

In order to explore further the difference in results for the HTN-NI group compared with the HTN-I and Con-S groups, we compared the neurocognitive test results of hypertension subjects who received antihypertensive medication to that of hypertension subjects who did not receive antihypertensive medication (regardless of categorization by BP improvement), in case ACE inhibition had a direct beneficial effect on cognition independent of its effect on BP. However, there was no significant difference in change in neurocognitive test scores between hypertensive subjects who received antihypertensive medication and those who did not (data not shown).

Discussion

We previously reported that subjects with untreated hypertension had lower performance in measures of verbal learning, memory, vocabulary, and manual dexterity compared with that of normotensive control subjects at baseline.(11) We now report that the neurocognitive test performance of the hypertension subjects improved after 1- year of antihypertensive therapy in some neurocognitive tests; in particular this was noted on measures of verbal learning and memory (RAVLT), manual dexterity (Grooved Pegboard), and executive function (DKEFS Tower Test). However, the test performance of the control subjects also improved to a

similar degree on these same measures, such that there was no significant difference in the change in scores between hypertension and control subjects after adjusting for potential confounders. The fact that the control group improved to a similar degree in these measures suggests that the improvement seen in the hypertension subjects may not have been due to the antihypertensive therapy, but instead to practice effects, the propensity of scores to improve on repeat testing due to learned strategies (21) or to normal growth in skills with age. These findings are consistent with results of clinical trials in adults, which do not clearly prove or disprove a beneficial effect of antihypertensive therapy, in the short term, on subsequent cognition.(7)

However, examination of the results by effectiveness of the antihypertensive treatment (according to ABPM results) suggests that the findings are more complicated. The secondary analyses differentiated between the hypertensive subjects with successful treatment of their hypertension (HTN-I) and the hypertensive subjects with unsuccessful treatment (persistent ambulatory hypertension, HTN-NI). Similar to results of the primary analyses, the hypertension subjects with successful treatment and the control subjects both had improvement in scores on the RAVLT (verbal learning and memory) at 1-year to a similar degree, suggesting significant practice effect or normal growth in skills with age. However, the hypertension subjects with poor control of their hypertension did not show the same improvement in scores on the RAVLT, suggesting that they did not have the same practice effect or normal growth in skills with age and continued to show the same neurocognitive profile at the end of treatment as at baseline. This finding suggests that poor hypertension control was associated with a blunted ability to recall learned strategies for improvement and/or to recall the content of test items. There was a similar pattern for the results on Grooved Pegboard (manual dexterity), where the subjects with poor hypertension control had blunted improvement in scores compared with successfully treated hypertension subjects and control subjects. The association between poor hypertension control and diminished practice effect or diminished growth in skills with age in some neurocognitive measures raises the concern that the adequacy of hypertension treatment may have an impact on cognition over time. Effective antihypertensive therapy appeared necessary for developmentally-expected growth in cognition over time to occur, suggesting that under-treated hypertension in youth may contribute to lower cognitive reserve and the beginnings of cognitive decline. With the epidemic of obesity and hypertension in youth, the path to these lower cognitive outcomes may be beginning ever earlier. A recent report from the Cardiovascular Risk in Young Finns Study was consistent with this scenario, showing that systolic hypertension in adolescence was associated with lower cognitive test performance in midlife.(5)

Our experience underscores important challenges to the study of cognition in hypertensive youth and the treatment of primary hypertension in children in general. The lost to follow-up rate of the hypertension group was high at 27%, despite significant study coordinator efforts to retain these subjects. Many of these subjects were not only lost to follow-up from the study, but also from clinical care (personal communication), a finding consistent with reports that, in the United States, young adults have the lowest hypertension control rates and visit adherence rates among adult age groups.(22, 23) Our findings demonstrate that visit and medication adherence is also a problem in an adolescent population with hypertension and

this factor might affect the impact of hypertension management. Data on the longitudinal treatment of children with primary hypertension are limited, but similar lost to follow-up rates have been reported.(24) The subjects who were lost to follow-up had higher parent ratings of executive dysfunction (BRIEF BRI scale) compared with that of subjects not lost to follow-up. The BRIEF BRI summary score evaluates the child's ability to control impulses, alter problem solving strategies, regulate attention, and modulate emotional responses in real life settings.(14, 25) Decreased executive functioning has been implicated as a factor in low medication adherence in chronic conditions in both adults and children.(26–28) One can postulate that lower executive functioning in the hypertensive adolescent could be associated with medication and visit non-adherence. This concern is a particular challenge for studies of cognition in hypertension as the subjects most likely to withdraw may be those of most interest.

Among the hypertension subjects who completed follow-up visits, approximately 30% (17 of 55) had inadequate control of their hypertension by ABPM. However, all but 4 of the 17 had normal office BP at the 1-year study visit, suggesting the presence of masked hypertension.(29) Masked hypertension occurs when patients have normal office BP but elevated BP by ABPM, and it is associated with increased risk for hypertensive target organ damage.(30) Others have described the persistence of sustained hypertension by ambulatory monitoring in children who appeared controlled by office readings.(31, 32) The use of ABPM for determining adequacy of hypertension control has been largely absent from adult studies of the effect of hypertension treatment on subsequent cognitive decline, a potential explanation, in part, for the inconsistencies in study results. Our results suggest that investigators and clinicians should consider monitoring the adequacy of hypertension treatment by ABPM rather than relying solely on office readings.

The current study has several limitations. The antihypertensive management was not administered in a strict protocol-driven manner across sites, but instead allowed for discretion of the site physician, albeit with some general standardization. Although this approach is closer to real world treatment, it did allow for some differences in treatment approach from patient to patient that could have had an impact on the neurocognitive outcomes. Hypertension subjects on antihypertensive medication were contacted monthly to encourage compliance whereas the hypertension subjects managed with lifestyle modification alone were not, a difference in approach which could have potentially led to a difference in compliance between these two groups. In accordance with national consensus guidelines at the time of study design, we relied on office manual BP to guide treatment. We did not perform interim ABPM to assess adequacy of treatment, an approach which would miss nocturnal hypertension and masked hypertension. Similarly, we did not assess compliance with the recommendation for dietary modification and regular exercise and we did not have a formal mechanism to measure medication compliance, factors with potential influence on neurocognitive test performance. Further, our initial sample size was small and our lost to follow-up rate among the hypertension group was relatively high, a situation which may have lessened our ability to detect changes in neurocognitive test performance with treatment. Although the secondary subgroup analyses suggested that subjects with successful hypertension treatment performed differently than those with unsuccessful treatment, these results need to be interpreted with caution due to the smaller sample size

and potential biases associated with subgroup analyses. In addition, there was relatively wide variability in the neurocognitive test scores with relatively small differences between groups, implying that serial neurocognitive testing alone may not be the most optimal method of detecting an effect of hypertension treatment on hypertensive target organ damage to the brain in youth. Our study did not include neuroimaging, an additional potential marker of hypertensive target organ damage, and these types of assessment procedures may have augmented our ability to detect changes over time. Lastly, we waited a full year before retesting in order to minimize practice effects. However, by waiting a year, we may have increased the chance of improvement in neurocognitive measures due to normal growth in skills with age. Both residual practice effect and normal growth in skills with age complicate the interpretation of the improvement in some of the neurocognitive tests in the hypertension group. Conversely, an interval of one year might not have allowed for sufficient evolution of differences between groups.

In summary, our data showed that 1-year of antihypertensive therapy did not improve the previously described lower neurocognitive test performance in hypertension subjects beyond the improvement also seen in control subjects over the same time period. However, the secondary analyses suggested that the effectiveness of antihypertensive therapy may have an impact on neurocognitive test performance by enabling hypertensive children to benefit from strategic learning to the same extent as nonhypertensive children. Further longitudinal research with larger numbers of subjects followed for longer periods of time are needed to determine the influence of BP control from youth on neurocognitive test performance during youth itself and on possible amelioration of cognitive decline over time. Future studies should utilize ABPM in hypertension treatment management and should include additional surrogate markers of central nervous system target organ damage, such as different types of neuroimaging, in order to address the important question of whether treating hypertension from adolescence would achieve improvement in subsequent cognitive outcomes.

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Table 1

Neurocognitive Test Battery

Neurocognitive Measures	Subtests	Cognitive Domain
Rey Auditory Verbal Learning Test (RAVLT)	List A Trial 1 * List A Total * List A Short Delay Recall * List A Long Delay Recall	Attention, learning, and memory Learning and memory Learning and memory Learning and memory
CogState Groton Maze Learning Task (GMLT)	GMLT Total Error GMLT Delayed Recall *	Planning/Problem Solving Memory
Wechsler Abbreviated Scales of Intelligence (WASI)	Vocabulary * Matrix Reasoning Full Scale IQ (FSIQ) *	General intelligence
Grooved Pegboard Test	Time to completion Dominant hand * Non-dominant hand	Fine motor dexterity
Delis-Kaplan Executive Function System (DKEFS), Tower Test	Total Achievement	Planning/Problem Solving
Wechsler Intelligence Scale for Children -4th ed (WISC-IV)	Digit Span Forward and Backward Spatial Span Forward and Backward	Working memory, Attention
CogState Set Shifting	Set Shifting Total Error	Set Shifting
Conners' Continuous Performance Test-II (CPT-II)	Omission Errors Commission Errors Variability Detectability	Attention and vigilance Response inhibition Attention Attention
Parent Behavior Rating Inventory of Executive Function (BRIEF)	Metacognition Index (MI) Behavior Regulation Index (BRI)	Behavioral correlates of executive function

* Measures previously reported to distinguish HTN from control subjects at baseline in the same cohort

Table 2

Baseline Demographic Characteristics

Characteristics	Normotensive controls (N = 66)	Hypertension subjects (N = 55)	*P* value
Age, y	15.3 ± 1.9	15.0 ± 2.3	0.35
BMI z score	1.88 ± 0.60	1.79 ± 0.80	0.50
Obese, %	71.2	63.6	0.43
African American, %	30.3	38.2	0.44
Hispanic, %	16.7	18.1	0.99
Maternal education, %			0.72
Less than high school	15.1	9.1	
High school	37.9	41.8	
College	40.9	40.0	
More than college	6.1	9.1	
Household income, %			0.03
Low	19.7	38.2	
Mid	48.5	27.3	
High	31.8	34.5	
Male, %	65.2	74.5	0.32
CRP, mg/L	2.57 ± 3.17	2.12 ± 3.23	0.45
HOMA-IR	5.4 ± 3.7	4.5 ± 3.3	0.15
Triglycerides, mg/dL	96 ± 59	112 ± 73	0.19
LDL cholesterol, mg/dL	88.8 ± 26	92.0 ± 32.5	0.55
HDL cholesterol, mg/dL	47.2 ± 11.5	46.2 ± 12.3	0.65
24-h SBP load, %	6.2 ± 6.2	57.6 ± 16.9	<0.001
24-h DBP load, %	5.3 ± 4.8	28.0 ± 17.6	<0.001

Table 3

ABPM and BMI measures at the baseline and 1-year assessments

	Normotensive controls N = 66			Hypertension N = 55		
Measure	**Baseline**	**1-year**	***P* value**	**Baseline**	**1-year**	***P* value**
dSBP index	0.87 ± 0.05	0.88 ± 0.06	0.07	1.02 ± 0.05	0.96 ± 0.06	< 0.001
dDBP index	0.80 ± 0.06	0.80 ± 0.06	0.83	0.91 ± 0.08	0.85 ± 0.07	< 0.001
nSBP index	0.87 ± 0.06	0.88 ± 0.06	0.02	1.02 ± 0.07	0.98 ± 0.10	0.014
nDBP index	0.82 ± 0.07	0.83 ± 0.08	0.22	0.95 ± 0.10	0.91 ± 0.11	0.013
24hr SBP load	6.2 ± 6.2	10.1 ± 10.1	0.001	57.6 ± 16.9	37.8 ± 26.3	< 0.001
24hr DBP load	5.3 ± 4.8	6.6 ± 6.0	0.098	28.0 ± 17.6	17.6 ± 13.2	< 0.001
BMI z-score	1.88 ± 0.60	1.80 ± 0.72	0.07	1.79 ± 0.80	1.80 ± 0.81	0.74

dSBP = daytime systolic BP index, dDBP = daytime diastolic BP index, nSBP = nighttime systolic BP index, nDBP index = nighttime diastolic BP index.

Table 4

ABPM parameters in hypertension and control subgroups

	Normotensive controls						Hypertension					
	Sustained Normotension N = 56			Developed Increased BP N = 10			Improved N = 38			Persistent Ambulatory Hypertension N = 17		
Parameter	**Baseline**	**1-year**	***P* value**	**Baseline**	**1-year**	***P* value**	**Baseline**	**1-year**	***P* value**	**Baseline**	**1-year**	***P* value**
dSBP index	0.86 ± 0.05	0.86 ± 0.05	0.88	0.88 ± 0.03	0.96 ± 0.03	<0.001	1.03 ± 0.05	0.93 ± 0.05	<0.001	1.01 ± 0.05	1.04 ± 0.04	0.07
dDBP index	0.80 ± 0.06	0.79 ± 0.06	0.40	0.79 ± 0.04	0.85 ± 0.06	0.008	0.91 ± 0.08	0.83 ± 0.06	<0.001	0.92 ±0.09	0.91 ± 0.05	0.99
nSBP index	0.86 ± 0.05	0.87 ± 0.06	0.14	0.91 ± 0.05	0.95 ± 0.05	0.025	1.00 ± 0.07	0.93 ± 0.07	<0.001	1.04 ± 0.08	1.08 ± 0.10	0.044
nDBP index	0.82 ± 0.07	0.83 ± 0.08	0.51	0.81 ± 0.06	0.86 ± 0.08	0.21	0.94 ± 0.09	0.87 ± 0.08	<0.001	0.98 ± 0.11	1.01 ± 0.12	0.11
24hr SBP load	5.4 ± 5.6	6.9 ± 6.6	0.12	11.0 ± 7.8	29.4 ± 5.2	<0.001	58.6 ± 15.8	24.5 ± 17.2	<0.001	55.4 ± 19.5	69.5 ± 14.0	0.005
24hr DBP load	5.5 ± 4.8	6.1 ± 6.0	0.40	4.5 ± 5.2	9.3 ± 5.1	0.24	26.8 ± 15.2	12.7 ± 9.2	<0.001	30.6 ± 22.2	29.3 ± 14.0	0.47

dSBP = daytime systolic BP index, dDBP = daytime diastolic BP index, nSBP = nighttime systolic BP index, nDBP index = nighttime diastolic BP index.

Table 5

Results of Primary Analyses of Neurocognitive Test Performance

Neurocognitive Measure	Group	Baseline	LSM change	Effect Size Within group
RAVLT (total correct, raw scores)				
	HTN	6.3	0.18	0.11
List A Trial 1	Con	6.7	0.35	0.22
	HTN	48.0	1.40	0.23
List A Total (Trials 1–5)	Con	53	2.07**	0.35
	HTN	9.4	0.73**	0.41
List A Short Delay Recall	Con	10.4	0.78***	0.44
	HTN	9.4	0.87**	0.43
List A Long Delay Recall	Con	10.3	1.17***	0.59
WASI (T scores)				
Vocabulary	HTN	47.5	−0.42	−0.07
	Con	50.5	0.12	0.02
Matrix Reasoning	HTN	48.9	2.5*	0.32
	Con	59.7	1.2	0.15
CogState GMLT				
GMLT Total Error	HTN	59.9	−0.18	0.12
	Con	56.1	−4.4*	0.28
GMLT Delayed Recall Error	HTN	9.6	−0.87	0.19
	Con	7.0	−1.46*	0.33
Grooved Pegboard (time, s)				
Dominant hand	HTN	84.3	−5.6***	0.59
	Con	78.0	−6.7***	0.71
Non-dominant hand	HTN	89.4	−4.9**	0.42
	Con	87.9	−7.1***	0.61
CPT–II (T scores)				
Omissions errors	HTN	49.6	1.7	−0.15
	Con	48.5	1.4	−0.12
Commissions errors	HTN	54.2	−1.3	0.15
	Con	52.1	−1.5	0.17
Variability	HTN	46.6	2.7	−0.24
	Con	46.3	3.4*	−0.31
Detectability	HTN	55.0	−1.6	0.19
	Con	51.9	−1.8	0.21
WISC-IV (scaled scores)				
Spatial Span Forward	HTN	9.1	−0.01	−0.01
	Con	9.3	1.03** †	0.40

Neurocognitive Measure	Group	Baseline	LSM change	Effect Size Within group
Spatial Span Backward	HTN	10.2	0.55*	0.31
	Con	10.3	0.21	0.12
Digit Span Forward	HTN	9.4	0.37	0.17
	Con	9.0	0.63*	0.30
Digit Span Backward	HTN	9.4	0.01	0.01
	Con	9.4	0.39	0.16
CogState Set Shift				
Total Error	HTN	38.5	−2.4	0.18
	Con	38.4	−4.6*	0.33
DKEFS Tower (scaled scores)				
Total Achievement	HTN	9.5	0.93**	0.40
	Con	9.2	0.85**	0.37
Parent BRIEF (T scores)				
BRI	HTN	48	−0.22	0.04
	Con	45.4	−0.01	0.01
MI	HTN	49.8	−1.2	0.18
	Con	48.4	−1.3	0.20

RAVLT = Rey Auditory Verbal Learning Test

WASI = Wechsler Abbreviated Scales of Intelligence

CogState GMLT = CogState Groton Maze Learning Test

CPT-II = Conners' Continuous Performance Test–II

WISC-IV = Wechsler Intelligence Scale for Children-IV

DKEFS Tower = Delis Kaplan Executive Function System Tower

Parent BRIEF = Parent Behavior Rating Inventory of Executive Function

BRI = Behavior Regulation Index

MI = Metacognition Index

HTN = Hypertension, all subjects, N = 55

Con = Control subjects, all subjects, N = 66

LSM = Least Square Means

Within group treatment differences, * $p < 0.05$, ** $p < 0.01$, ***$p < 0.001$

Between group comparisons, † = $p < 0.05$ for HTN vs. Con

Sign (+/−) of effect size oriented such that positive values indicate better performance in relation to baseline and vice versa

All comparisons adjusted for age, sex, maternal education, race, income, BMI z-score at baseline, change in BMI z-score in 1 year, Pediatric Sleep Questionnaire, and HOMA (HOMA is a measure of insulin resistance).

Table 6

Results of Neurocognitive Test Performance by Effectiveness of Antihypertensive Treatment

Neurocognitive Measure	Group	Baseline	LSM change	Effect Size Within group
RAVLT (total correct, raw scores)				
List A Trial 1	HTN I	6.5	0.50†	0.32
	HTN NI	5.9	−0.48	−0.29
	Con-S	6.6	0.57**†	0.37
List A Total (Trials 1–5)	HTN I	48.3	2.7**†	0.46
	HTN NI	46.4	−1.4	−0.23
	Con-S	50.2	2.3**†	0.38
List A Short Delay Recall	HTN I	9.1	0.89**	0.50
	HTN NI	9.6	0.23	0.12
	Con-S	10.6	0.74**	0.41
List A Long Delay Recall	HTN I	9.3	0.98**	0.49
	HTN NI	9.1	0.64	0.30
	Con-S	10.4	1.1***	0.56
WASI (T scores)				
Vocabulary	HTN I	47.6	−0.36	−0.06
	HTN NI	47.1	−0.68	−0.12
	Con-S	50.9	0.44	0.08
Matrix Reasoning	HTN I	48.7	2.2	0.28
	HTN NI	49.6	3.1	0.39
	Con-S	50.3	0.11	0.01
CogState GMLT				
GMLT Total Error	HTN I	59.4	−1.6	0.10
	HTN NI	60.1	−3.5	0.21
	Con-S	57.2	−3.9	0.24
GMLT Delayed Recall Error	HTN I	8.8	−1.2	0.27
	HTN NI	11.7	−0.75	0.15
	Con-S	7.4	−1.4*	0.29
Grooved Pegboard (time, s)				
Dominant hand	HTN I	83.7	−7.3***	0.78
	HTN NI	85.3	−2.7	0.27
	Con-S	78.0	−6.8***	0.70
Non-dominant hand	HTN I	87.7	−6.5***	0.61
	HTN NI	92.8	−1.6	0.14
	Con-S	87.3	−7.4***	0.69
CPT–II (T scores)				
Omissions errors	HTN I	48.2	2.7	−0.23
	HTN NI	52.4	−1.6	0.12

Neurocognitive Measure	Group	Baseline	LSM change	Effect Size Within group
	Con-S	48.7	1.8	−0.15
Commissions errors	HTN I	52.8	−1.7	0.20
	HTN NI	56.4	−1.2	0.12
	Con-S	52.7	−1.7	0.19
Variability	HTN I	46.1	4.9**†	−0.45
	HTN NI	47.6	−2.0	0.17
	Con-S	45.9	3.9**	−0.36
Detectability	HTN I	53.5	−2.1	0.26
	HTN NI	57.4	−1.0	0.11
	Con-S	52.7	−1.8	0.21
WISC-IV (scaled scores)				
Spatial Span Forward	HTN I	9.4	0.05	0.02
	HTN NI	8.3	−0.17	−0.06
	Con-S	9.2	1.2**	0.45
Spatial Span Backward	HTN I	10.5	0.52	0.30
	HTN NI	10.1	0.48	0.28
	Con-S	10.6	0.17	0.10
Digit Span Forward	HTN I	9.9	0.26	0.12
	HTN NI	8.6	0.42	0.18
	Con-S	9.1	0.53	0.25
Digit Span Backward	HTN I	9.4	−0.07	−0.03
	HTN NI	9.6	0.13	0.05
	Con-S	9.5	0.33	0.13
CogState Set Shift				
Total Error	HTN I	36.2	−3.1	0.22
	HTN NI	43.9	−0.42	0.03
	Con-S	38.4	−3.7	0.26
DKEFS Tower (scaled scores)				
Total Achievement	HTN I	9.3	0.82*	0.35
	HTN NI	10.3	1.2	0.48
	Con-S	9.3	0.85**	0.36
Parent BRIEF (T scores)				
BRI	HTN I	48.2	−1.0	0.16
	HTN NI	48.5	1.4	−0.20
	Con-S	45.8	0.07	−0.01
MI	HTN I	48.4	−1.6	0.23
	HTN NI	49.2	−0.12	0.02
	Con-S	48.4	−1.0	0.16

RAVLT = Rey Auditory Verbal Learning Test

WASI = Wechsler Abbreviated Scales of Intelligence CogState

GMLT = CogState Groton Maze Learning Test

CPT-II = Conners' Continuous Performance Test–II

WISC-IV = Wechsler Intelligence Scale for Children-IV

DKEFS Tower = Delis Kaplan Executive Function System Tower

Parent BRIEF = Parent Behavior Rating Inventory of Executive Function

BRI = Behavior Regulation Index

MI = Metacognition Index

HTN I = Hypertension improved, N = 38

HTN NI = Hypertension not improved, N = 17

Con-S = Control subjects with sustained normotension over the year, N = 56

LSM = Least Square Means

Within group treatment differences, * $p < 0.05$, ** $p < 0.01$, ***$p < 0.001$

Between group comparisons, † = $p < 0.05$ for HTN or Con-S vs HTN NI

Sign (+/−) of effect size oriented such that positive values indicate better performance in relation to baseline and vice versa

All comparisons adjusted for age, sex, maternal education, race, income, BMI z-score at baseline, change in BMI z- score in 1 year, Pediatric Sleep Questionnaire, and HOMA (HOMA is a measure of insulin resistance).