Published in final edited form as:
Pediatr Nephrol. 2013 March ; 28(3): 401–408. doi:10.1007/s00467-012-2215-8.

Primary Hypertension and Neurocognitive & Executive Functioning in School-aged Children

Juan C. Kupferman, MD, MPH[1], **Marc B. Lande, MD, MPH**[2], **Heather R. Adams, PhD**[3], and **Steven G. Pavlakis, MD**[4]

[1]Division of Pediatric Nephrology and Hypertension, Department of Pediatrics, Maimonides Medical Center, Brooklyn, NY

[2]Division of Pediatric Nephrology, Department of Pediatrics, Golisano Children's Hospital, University of Rochester Medical Center, Rochester, NY

[3]Division of Child Neurology, Department of Pediatrics, Golisano Children's Hospital, University of Rochester Medical Center, Rochester, NY

[4]Center for Brain and Behavior, Maimonides Medical Center, Brooklyn, NY

Abstract

Data on neurocognitive function in hypertensive children are very limited. In this review, we summarize recent preliminary, early studies that suggest that children with elevated blood pressure demonstrate evidence of worse performance on direct neurocognitive testing, as well as evidence of executive dysfunction based on parent ratings, compared to matched normotensive comparison groups. Furthermore, hypertensive children may also have increased prevalence of learning disabilities as well as a blunted cerebrovascular reactivity compared to normotensive controls. Larger, prospective studies are needed to confirm and further explore these emerging but preliminary findings.

Keywords

cognition; elevated blood pressure; brain; pediatric; executive function; memory

INTRODUCTION

As pediatric hypertension is on the rise (1,2), there has been increased interest in evaluating its impact on both the disease and its treatment on neurocognitive function (3–7). At present, data on neurocognitive function in hypertensive children are very limited. The objectives of this review are to summarize the current knowledge of neurocognitive function in hypertensive children, to review possible pathophysiological mechanisms and to discuss the implications of such early subclinical manifestations of elevated blood pressure (BP) in the context of children's education and future cardiovascular health.

Articles for this review were chosen by searching Pubmed database, reviewing reference sections of seminal articles and recommendations from content experts. The manuscript follows a structured format (definitions of executive functions and neurocognitive assessment, summary of the adult and pediatric literature on the relationship between hypertension and cognitive function, summary of adult and child literature on the impact of

Correspondence: Juan C. Kupferman, MD, MPH, Director, Division of Pediatric Nephrology and Hypertension, Maimonides Medical Center, 977 48th Street, Brooklyn, NY 11219, Phone 718-283-6165, Fax 718-283-6268, jkupferman@maimonidesmed.org.

treatment of hypertension on improvement of cognitive functioning, description of the literature hypothesizing the pathophysiology of the damage, conclusions and recommendations) that will facilitate understanding of a topic usually not covered in a pediatric nephrology journal.

DEFINITIONS

Neurocognitive assessment

The core function of neurocognitive (also called ‘neuropsychological’) assessment is to understand brain-behavior relationships – that is, the associations of brain structure and function to cognition and behavior. Neurocognitive assessment is used to evaluate the impact of neurological disease or injury upon learning and behavior, describe neurocognitive phenotypes associated with disease or injury, or monitor change over time in progressive disorders with central nervous system effects. Neurocognitive studies of hypertensive adults and children have focused principally on cognitive domains of attention and working memory, executive functions (EF), and recall of newly learned information.

Executive Functions

EF refer to higher cognitive activities that include skills needed for purposeful, goal-directed behavior. EF are thought to not be in maximal use during routine, previously learned tasks, but instead are invoked during novel complex tasks where no established routines exist (8,9). The construct of EF is broad but encompasses organization and planning, problem solving, abstract reasoning, impulse control, and flexible thinking. EF “*emphasize the metacognitive capacities that allow an individual to perceive stimuli from his or her environment, respond adaptively, flexibly change direction, anticipate future goals, consider consequences, and respond in an integrated or common-sense way, utilizing all these capacities to serve a common purposive goal* [sic]” (10). In everyday life, decreased EF can manifest as inappropriate social behavior, trouble with organization distractibility, or problems with decision making, making sound judgments, or remembering to implement future tasks (8,9). EF skills develop throughout the adolescent and young adult years and this development corresponds to maturational brain changes in prefrontal cortex and connectivity of prefrontal regions with other cortical and subcortical regions (11). Neurocognitive assessment of EF skills has been conventionally evaluated with performance-based laboratory measures (e.g., computerized or paper-and-pencil tests on discrete tasks). However, executive dysfunction, particularly when there are subtle decrements in performance, may not manifest in the structured, quiet, and one-on-one testing environment of laboratory based testing. Therefore, EF assessment now often also incorporates information on everyday settings where EF demands are greater (8,12). The Behavior Rating Inventory of Executive Function (BRIEF), a measure used in two of the pediatric studies discussed below, is a questionnaire that evaluates behavioral correlates of EF by raters who have observed the child during everyday life (teachers and parents), and for teens, can also incorporate self-ratings of EF (13). BRIEF items address common everyday EF tasks such as remembering to turn in homework assignments, or the ability to attend to and complete a set of multi-step instructions. These items are organized statistically and conceptually into two constructs, or indices: the Behavior Regulation Index (BRI) and the Metacognition Index (MI), and an overall summary score (encompassing all items): the Global Executive Composite (GEC) (13). Results are reported as sex and age-normed T-scores (mean = 50, SD = 10), with higher scores indicating greater EF dysfunction in relation to peers (14). As well, computerized cognitive test batteries can detect more subtle differences in EF performance under timed conditions.

HYPERTENSION AND COGNITIVE FUNCTION

Neurocognitive studies in adults—Subtle changes in the brain may long precede acute hypertensive events, just as left ventricular hypertrophy can be an early manifestation of cardiac target organ damage, long preceding the development of myocardial infarction or congestive heart failure (15). As an example, adults with primary hypertension have lower scores on tests of neurocognitive performance in comparison to matched normotensive controls. Some of the largest and most consistent effects are noted within the domains of learning and memory, attention, abstract reasoning, and EF (15). For example, hypertensive groups perform less well on tasks where they are required to learn and remember word lists, attend to and repeat verbatim lengthy number sequences, attend to specific visual stimuli (e.g., 'seek and find' tasks), or identify relationships among abstract pictures or concepts (i.e., *how are these the same?',* or *'sort these into groups'* tasks) (15, 16). There is also evidence, though less consistent, for worse performance by hypertensive compared to normotensive groups in tests of visual perception (e.g., matching images to one another or identifying pictures based on partial information), visuoconstructional abilities (e.g., copying two- or three-dimensional images using blocks, completing jigsaw-style puzzles), psychomotor speed and fine motor dexterity (e.g., quickly completing line tracings, rapid finger tapping, setting small pegs into holes) (16). Decreased performance on neurocognitive testing has even been reported in adult subjects with systolic BP (SBP) in the high normal range (17). Review of the studies on neurocognitive testing in adult hypertension yields several central observations. First, performance deficits in tests of EF and working memory (a component of EF) feature most prominently and consistently across studies, regardless of sample characteristics or methodology. Second, while differences between hypertensives and normotensives are found, few of those with hypertension are classified as cognitively impaired. Instead, the differences between groups occur largely in the normal range of the neurocognitive tests (18). Lastly, while the relationship between hypertension and cognition has been noted in all adult age groups, several reports have shown a more pronounced difference in neurocognitive test performance between hypertensive and normotensive young adult subjects, in comparison to studies of middle-aged or older hypertensive adults (17,18), an observation that lends biological plausibility to the possibility that there may be a similar hypertension-cognition link in children.

Neurocognitive studies in children—There is emerging, preliminary evidence that hypertensive children also manifest lower neurocognitive test performances in comparison to normotensive control subjects. The relationship between elevated BP and neurocognitive test performance in children was first investigated in a cross-sectional analysis of 5077 children 6 to 16 years-old who participated in the National Health and Nutrition Examination Survey III (NHANES III), a nationally representative sample of US children and adults (3). Children in NHANES III had casual BP measurement and were administered four neurocognitive subtests, including Digit Span, a test of working memory and attention, and Block Design, a test of constructional skills, from the Wechsler Intelligence Scale for Children, Revised as well as Reading and Arithmetic sections from the Wide Range Achievement Test, Revised. Children with SBP > 90th percentile had lower average scores compared with normotensive children for Digit Span (7.9 vs. 8.7, p = 0.01), Block Design (8.6 vs. 9.5, p = 0.03), and Mathematics (89.6 vs. 93.8, p = 0.01). Elevated diastolic BP (DBP) was associated with lower average scores on Block Design only (9.5 vs. 11, p = 0.01). After controlling for socioeconomic status, obesity, and other demographic factors, SBP ≥ 90th percentile was independently associated with decreased performance on Digit Span (p = 0.030). In addition, the decrease in Digit Span scores was more prominent for children with SBP ≥95th percentile, suggesting a dose effect of elevated SBP on test performance.

In a subsequent prospective single center study, parental assessment of behavior and EF (parent BRIEF; discussed above - Definitions, Executive Functions section) of 32 children with sustained hypertension (confirmed by ambulatory BP monitoring) was compared to that of 31 normotensive controls (6). The groups were proportionally matched for sex, age, race, obesity, household income, maternal education, and IQ. Hypertensive children were found to have decreased EF as manifest as higher (worse) scores on the parent BRIEF (BRI: 51 vs. 42.5, $p = 0.014$, MI: 51 vs. 44, $p = 0.031$, GEC: 50 vs. 43, $p = 0.009$) (8). Similar to findings in adults, the differences in EF between hypertensive and normotensive children occurred largely in the normal range of the rating scale, meaning that the hypertensive children were not found to be cognitively impaired (6). Notably, the finding of decreased performance in measures of EF and working memory (a component of EF) found in these studies parallels findings of studies of cognition in hypertensive adults (18).

Another recent report showed that children with hypertension are also more likely to be diagnosed with a learning disability, suggesting that hypertensive children are at increased risk for academic difficulties (7). Two hundred and one consecutive children aged 10 – 18 years who were referred for the evaluation of elevated BP were categorized as having either sustained hypertension (n = 100) or prehypertension (n = 101). The children with sustained hypertension were more likely than those with prehypertension to be receiving special education services at school for a learning disability (18% vs. 9%, $p < 0.001$) and in adjusted analysis, the odds of the diagnosis of learning disability was four times higher in hypertensive children. In addition, the children with sustained hypertension were more likely to have attention deficit disorder (ADHD), defined as being on medication for ADHD (27% vs. 7%, $p = 0.007$). The authors acknowledged that medications prescribed for ADHD can raise BP and also that ADHD and learning disability frequently occur together (7). The authors discussed that the higher prevalence of ADHD in the sustained hypertension group could have been influenced by the effect of ADHD medications on BP. However, the increased prevalence of ADHD in the hypertensive group could also be an additional manifestation of neurocognitive difficulties among children with hypertension. Regardless, the finding of increased prevalence of learning disability in children with sustained hypertension remains robust even after excluding children with ADHD from the analysis.

Taken together, the findings of the above studies of increased prevalence of learning disability in children with sustained hypertension, lower scores on Digit Span (a measure of working memory) in children with elevated BP in NHANES, and worse parental ratings of EF on the BRIEF in children with sustained hypertension all support the notion that children with hypertension may be at risk for deficits in EF.

The above studies report on cognition in children with elevated BP. Ditto and colleagues have extended this area of investigation by evaluating cognition in children with BP in the high normal range (4). In a post-hoc analysis of data from a longitudinal study of the development of aggression in males, the investigators administered an extensive neurocognitive battery to 88 normotensive 14-year-old boys. Boys with both a parental history of hypertension and high normal BP were at increased risk for lower scores on a verbal learning factor (including digit span tasks) and boys with high normal BP also had significantly lower scores on measures of spatial learning. These results are consistent with studies of normotensive adults with a parental history of hypertension showing that they have lower average scores on neurocognitive testing compared with scores of normotensive adults without a parental history of hypertension, but that the affected neurocognitive domains differ from that of adults who have hypertension (16).

Evidence for an association between elevated BP and decreased academic performance was also found in a study of the effect of cardiovascular risk factors and performance on

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standardized academic state testing in 968 fifth-grade students in West Virginia (5). After adjusting for body mass index, socioeconomic status, sex, diet, and fitness, elevated BP was significantly associated with decreased scores on the science subtest (F = 13.19, p = 0.044). By contrast, there was no association between elevated BP and scores in the reading/ language arts, mathematics, or social studies subtests.

Obesity, a common comorbidity with hypertension, has itself been associated with decreased EF in adults, although studies of this association in children are conflicting (19). Furthermore, obese children are at increased risk for obstructive sleep apnea, an entity also associated with decreased performance on neurocognitive testing and academic difficulties (20). These observations underscore the importance of adjusting for the potential effects of obesity in studies of hypertension and cognition.

Together, the above studies provide early, preliminary evidence that children with elevated BP demonstrate neurocognitive differences when compared to normotensive controls. The cross sectional nature of these preliminary studies does not allow inference as to whether elevated BP leads to neurocognitive issues (possibly as a subtle manifestations of hypertensive target organ to the brain) versus the possibility that children with neurocognitive deficits may be more likely to develop primary hypertension, a disease known to be in part centrally mediated. Table 1 summarizes neurocognitive studies in children with elevated BP.

While differences in study methods and neurocognitive measures used do complicate interpretation of results across studies, there is general convergence that hypertensive groups perform less well than normotensives on various tasks of attention, memory, and EF. Ongoing, multi-center research with consistent neurocognitive test protocols, replication of prior investigations, and the use of sensitive computerized cognitive tests that also remove examiner variability, will further increase consistency of findings across studies.

Effect of Treatment of Hypertension on Cognition

Studies in adults—If the performance deficits seen in patients with hypertension do represent an early manifestation of target organ damage to the brain, then this would imply that such deficits might be reversible with anti-hypertensive treatment. However, results of adult studies on the effect of anti-hypertensive medication on cognition have been inconsistent in the existence and direction of drug effects (21,22). These studies have often focused on middle-aged and older adults and were, thereby, limited by the potential confounding variable of advancing age.

In a study focused on young adults in which neurocognitive assessment was performed at baseline and again after 15 months of antihypertensive therapy, hypertensive subjects in whom BP was effectively lowered showed significant restoration of performance scores toward the levels of normotensive subjects (23). In a more recent study, Muldoon and colleagues found that a short-term 6-week course of various antihypertensive agents (atenolol, metoprolol, methyldopa, thiazide, enalapril, or verapamil) slightly improved performance on tests of memory but also resulted in small decrements in psychomotor speed, without drug class differences (24).

Studies in children—Data on the effects of antihypertensive therapy on neurocognitive test performance in children are very limited. A recent study reported on EF in children at baseline and after 12-months of antihypertensive therapy (25). The participants in this study were the subjects from the prior study of baseline parental assessments of EF described above whom subsequently returned for reassessment after 12 months. During the 12-month interval between study visits, the subjects with hypertension received standard of care

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antihypertensive therapy (therapeutic lifestyle modification counseling, angiotensin converting enzyme inhibition). Parents of children in the hypertensive and normotensive control study groups completed the BRIEF questionnaire at baseline and again at 12 months. While the number of subjects with both baseline and 12-month data was small (hypertensives, n = 22; controls, n = 25), the parent ratings of behavioral correlates of EF on BRIEF did improve significantly after therapy in the subjects with hypertension, after controlling for age, maternal education, and household income (baseline vs. 12-months, BRI, 50.3 vs. 46.2, p = 0.01; MI, 52.4 vs. 46.3, p < 0.01; GEC, 52.1 vs. 46.1, p < 0.01). By contrast, the parent ratings of EF of the control subjects did not change in the 12-month period. Furthermore, hypertensive subjects with baseline left ventricular hypertrophy or SBP load ≥ 50% were more likely to show improvement in EF after antihypertensive therapy, suggesting that it was the subjects most at risk for hypertensive target organ damage who had improvement in cognition with BP lowering. The authors concluded that their results lent support to the hypothesis that the neurocognitive deficits seen in children with primary hypertension represent hypertensive target-organ effects and that these deficits are, in part, reversible with anti-hypertensive therapy (25).

Potential Mechanisms

Studies of Cerebrovascular Reactivity—Hypertension can affect small vessels, resulting in vascular remodeling and impairment of cerebral blood flow regulation (26). The so-called “vascular hypothesis” of cognitive dysfunction in hypertension postulates that as cognitive processing elicits a regional distribution of blood flow, providing metabolic support to active neural areas, interference with this redistribution or decreased ability to enhance cerebral blood flow in response to increased neuronal activity might underlie the cognitive deficits of hypertensive individuals (27). However, an alternative hypothesis has suggested the possibility that the brain is affected before the blood vessels are affected (28).

Cerebrovascular reactivity (CVR) reflects the capacity of cerebral blood vessels to dilate in response to different factors and may be an important marker for brain vascular reserve. Several analyses using different reactivity stimuli (e.g., carbon dioxide, hyperventilation) and different methods to assess cerebral hemodynamics (e.g., transcranial Doppler [TCD], functional magnetic resonance imaging) have attempted to characterize the physiological association between hypertension and CVR, mostly in adults (29,30).

The effects of hypertension on CVR in children have been studied by TCD, a non-invasive procedure, to assess changes in cerebral blood flow in response to different stimuli (Table 2). Settakis and colleagues studied CVR in 113 hypertensive (mean age 16.4 years) and 58 normotensive (mean age 15.8 year) adolescents at rest and after 30 seconds of breath-holding, as a vasodilatory stimulus (31). Hypertension was defined by the average of 9 casual BP measurements obtained on 3 different occasions. The middle cerebral artery (MCA) was insonated through the temporal window on both sides. Resting peak, systolic, mean and diastolic blood flow velocities in the MCA of hypertensive adolescents were significantly higher than those of normotensive controls. The observed differences in blood flow velocity parameters disappeared after the breath-holding tests (systolic 122.2 ± 23.7 vs. control 114.8 ± 27.6, p = 0.07; mean 75.1 ± 19.5 vs. control 73 ± 21.2, p = 0.63; diastolic 52.0 ± 16.4 vs. control 53.1 ± 16, p = 0.67). The authors concluded that hypertensive subjects showed decreased vasodilatory capacity in response to hypercapnia reflecting impaired CVR compared to normotensive controls. In a subsequent study, these investigators assessed CVR responses on the same study population by using voluntary hyperventilation to induce hypocapnia as a vasoconstrictory stimulus (32). Assessment was made by TCD at rest and after 60 seconds of hyperventilation. It was found that hyperventilation induced a more pronounced percent change of the systolic and diastolic blood flow velocities of the control than in hypertensive subjects (systolic 21.0 ± 19.0 vs. control 25.9 ± 12.5, $p < 0.05$; mean 32.3 ± 14.7 vs. control 35.6 ± 15.8, $p = 0.18$; diastolic 40.4 ± 18.1 vs. control 45.5 ± 15.2, $p < 0.05$). The authors concluded that CVR to hypocapnia was also decreased in hypertensives compared to normotensive controls. One limitation of these initial studies was the lack of measuring end-tidal pCO_2 in the study population.

Páll and colleagues divided subjects according to 24-hour ambulatory blood pressure findings (33). Seventy-three subjects with hypertension (HTN) (mean age 16.5 years) and 47 with white-coat hypertension (wcHTN) (mean age 16.3 years) were compared to 59 normotensive controls (mean age 15.8 years). CVR was assessed by TCD breath-holding test and expressed in percent change to the resting cerebral blood flow velocity value. These investigators found that the percent increase in MCA mean blood flow velocity after 30 seconds of breath-holding was lower in both wcHTN (5.3 ± 3.1%) and HTN (9.5 ± 2.6%) groups indicating lower vasodilatory reactivity to carbon dioxide (CO_2) compared to normotensive controls (12.1 ± 2.2%), also suggesting involvement of the cerebral arterioles.

Wong and colleagues studied 56 children and adolescents (mean age 15.3 years) with HTN, prehypertension or wcHTN (diagnosed by 24-hour ambulatory pressure monitoring), compared to controls, by TCD examinations of the MCA while rebreathing CO_2 (34). A capnometer was utilized to measure end-tidal CO_2 ($ETCO_2$). Time-averaged maximum mean (TAMM) cerebral blood flow velocity measurements were obtained with increasing $ETCO_2$ at 10-second-intervals for 80 to 260 seconds. TAMM and $ETCO_2$ were used to quantify CVR reactivity during hypercapnia. The authors found that young subjects with untreated hypertension had significantly lower hypercapneic reactivity than normotensive controls (2.556 ± 1.832 cm/sec/mm Hg vs. 4.256 ± 1.334 cm/sec/mm Hg, $p<0.05$) (35). They also found that the baseline mean DBP z-scores ($r = -0.331$, $p = 0.037$) were inversely related to reactivity, suggesting that DBP may be a better predictor of cerebral end organ damage than SBP (35). Of note, the same relationship between DBP and cognitive impairment has also been documented in adults (34).

In children, there are no published studies addressing the effects of elevated BP on both CVR and cognition. Alterations in cerebral blood flow and possible neurocognitive deficits have been described in other diseases, such as in sickle cell disease and with mild-disordered breathing (36,37). Investigators have suggested that the neurocognitive deficits described in children and adolescents with hypertension may be secondary to abnormal CVR (35). Ongoing research will help clarify the relationship among elevated BP, abnormal CVR and neurocognitive deficits in children and adolescents.

Other potential contributing factors that have been associated with both hypertension and decreased cognition include autonomic nervous system dysregulation (38,39), hyperinsulinemia and hyperlipidemia (17), chronic inflammation (40,41), and genetic predisposition (42).

In summary, preliminary studies have showed a blunted reactivity response to hypercapnia, indicating a deranged vasodilatory reactivity in untreated hypertensive children and adolescents. These studies have many limitations, especially the low numbers of subjects. Whether these effects of hypertension on the cerebral vessels are cause and effect is unknown as it may just be an epiphenomenon. Further studies are needed to elucidate it.

Conclusions

The studies summarized in this review provide preliminary, early evidence that children with hypertension demonstrate deficits on measures of neurocognition, have an increased prevalence of learning difficulties, and have decreased CVR when compared with normotensive controls. However, the available studies are limited to database studies, small single-center prospective studies, and post hoc analyses. While the results to date are consistent with previous findings in young hypertensive adults (where performance deficits on measures of working memory and EF are prominent), larger prospective studies with more extensive measures of EF are needed to determine the true extent of any potential associations between hypertension and cognition in children and whether such associations change with antihypertensive therapy. In the meantime, clinicians should be aware of these emerging concerns, and should consider referral for neurocognitive testing for children with hypertension who are struggling academically.

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Table 1

Neurocognitive studies in children with hypertension

Year	Author	Design	Age	n	Main Findings	Tests Used
2003	Lande et al. (ref. 3)	cross-sectional post hoc analysis of database	6–16y	5077 participants in NHANES III, 217 with systolic BP >90th percentile, 85 with diastolic BP >90th percentile	SBP >90th associated with decreased performance in attention and working memory tests	Block design and digit span subtests of the Wechsler Intelligence Scale for Children, Revised (WISC-R) Reading and arithmetic sections of the Wide Range Achievement Test, Revised (WRAT-R)
2006	Ditto et al. (ref. 4)	prospective	14 y	88 normotensive boys	parental history of hypertension and high normal BP had lower scores on measures of verbal learning	Block design and vocabulary subtests of the Wechsler Intelligence Scale for Children, Revised (WISC-R) Paired associates and digit span subtests of the Wechsler Memory Scale, Revised Smith and Milner's Spatial Memory test Self-ordered Pointing and Nonspatial Conditional Association tasks Strategic Problem Solving and Subjective Ordering tasks Lezak's Letter Fluency and Semantic Fluency tests
2007	Cottrel et al. (ref. 5)	cross-sectional post hoc analysis of database	5th graders	968 students	elevated BP associated with decreased scores in science subtest	West Virginia Educational Standard Test (WESTEST)
2009	Lande et al. (ref. 6)	prospective	10–18 y	32 with hypertension 31 with normal BP	hypertensive children had decreased executive functioning	Block design and vocabulary subtests of WISC (ages 10–15) or the Wechsler Adult Intelligence Scale (ages ≥ 16) Achenbach Child Behavior Checklist (CBCL) Behavior Rating Inventory of Executive Function (BRIEF)
2010	Adams et al. (ref. 18)	retrospective	10–18 y	100 with hypertension 101 with prehypertension	children with hypertension more likely to be diagnosed with a learning disability	
2010	Lande et al. (ref. 25)	prospective	10–18 y	22 with hypertension 25 with normal BP	executive function scores improved after therapy in subjects with hypertension	Block design and vocabulary subtests of WISC (ages 10–15) or the Wechsler Adult Intelligence Scale (ages ≥ 16) Achenbach Child Behavior Checklist (CBCL) Behavior Rating Inventory of Executive Function (BRIEF)

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Table 2

Transcranial studies in children and adolescents with hypertension

Year	Author	Design	Age	n	Main findings
2003	Settakis and colleagues (ref. 30)	prospective	adolescents	58 normotensives 113 hypertensives	decreased cerebrovascular reactivity to hypercapnia in hypertensives
2006	Settakis and colleagues (ref. 31)	prospective	adolescents	58 normotensives 113 hypertensives	decreased cerebrovascular reactivity to hypocapnia in hypertensives
2011	Páll and colleagues (ref. 32)	prospective	adolescents	59 normotensives 47 white coat hypertensives 73 sustained hypertensives	both white-coat and sustained hypertensives had decreased vasodilatory reaction to carbon dioxide
2011	Wong and colleagues (ref. 33)	prospective	64 subjects 7–20 y	9 normotensives 9 prehypertensives 18 white-coat hypertensives 13 hypertensives	untreated hypertensives children and adolescents had a blunted reactivity to hypercapnia, indicating deranged vasodilatory reactivity