Cognitive Effects of Adenotonsillectomy for Obstructive Sleep Apnea

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abstract

OBJECTIVE: Research reveals mixed evidence for the effects of adenotonsillectomy (AT) on cognitive tests in children with obstructive sleep apnea syndrome (OSAS). The primary aim of the study was to investigate effects of AT on cognitive test scores in the randomized Childhood Adenotonsillectomy Trial.

METHODS: Children ages 5 to 9 years with OSAS without prolonged oxyhemoglobin desaturation were randomly assigned to watchful waiting with supportive care (n = 227) or early AT (eAT, n = 226). Neuropsychological tests were administered before the intervention and 7 months after the intervention. Mixed model analysis compared the groups on changes in test scores across follow-up, and regression analysis examined associations of these changes in the eAT group with changes in sleep measures.

RESULTS: Mean test scores were within the average range for both groups. Scores improved significantly ($P < .05$) more across follow-up for the eAT group than for the watchful waiting group. These differences were found only on measures of nonverbal reasoning, fine motor skills, and selective attention and had small effects sizes (Cohen's d, 0.20–0.24). As additional evidence for AT-related effects on scores, gains in test scores for the eAT group were associated with improvements in sleep measures.

CONCLUSIONS: Small and selective effects of AT were observed on cognitive tests in children with OSAS without prolonged desaturation. Relative to evidence from Childhood Adenotonsillectomy Trial for larger effects of surgery on sleep, behavior, and quality of life, AT may have limited benefits in reversing any cognitive effects of OSAS, or these benefits may require more extended follow-up to become manifest.

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WHAT'S KNOWN ON THIS SUBJECT: Research indicates variable but possibly selective effects of adenotonsillectomy (AT) on cognitive test scores in children with obstructive sleep apnea syndrome. However, few if any studies have examined changes after AT in a randomized trial assessing diverse cognitive skills.

WHAT THIS STUDY ADDS: Findings confirm small, selective effects of AT on cognitive test scores in a randomized trial of AT compared with nonsurgical management, as well as associations of pre-AT to post-AT gains in scores with improvement on measures of sleep disturbance.

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Childhood obstructive sleep apnea syndrome (OSAS) is characterized by intermittent upper airway obstruction that disrupts normal ventilation during sleep and sleep patterns.[1] The prevalence of OSAS is ~1% to 6%, with higher rates in African Americans and children from families of lower socioeconomic status.[2–4] Children with untreated OSAS are at risk for adverse outcomes ranging from daytime sleepiness and compromised cardiovascular health to behavior problems and impairments in cognition and academic performance.[5–11] Problems in behavior and emotional regulation are common in children with OSAS compared with healthy controls, but evidence for adverse effects of OSAS on children's cognitive abilities is more mixed.[6] Some studies fail to find differences between children with OSAS and healthy controls,[12,13] and those that do report variable associations of measures of sleep disturbance with cognitive test scores.[7,14–18] Similarly, studies of outcomes of adenotonsillectomy (AT) in children with OSAS indicate variable benefits on such tests, with little evidence for associations of these effects with the severity of OSAS and sleep disruption.[8,13,14,16,19–26]

In the recently completed multicenter Childhood Adenotonsillectomy Trial (CHAT), children with OSAS without prolonged oxyhemoglobin desaturation assigned to early AT (eAT) improved more than those assigned to watchful waiting with supportive care (WWSC) on key secondary outcomes.[27–29] Specifically, the eAT group improved more than the WWSC group from a baseline preintervention assessment to a 7-month postintervention follow-up on polysomnographic indices and symptoms of OSAS, global indices of behavior, and quality of life, but not on the primary cognitive outcome measure (A Developmental Neuropsychological Assessment [NEPSY] Attention and Executive Function Domain score) or on global cognitive ability. However, the individual tests that make up these 2 composite measures and other tests predesignated as secondary measures of outcome were not examined for their sensitivity to the effects of AT. Examination of these measures was warranted to determine potential benefits of AT on specific cognitive skills and identify measures sensitive to the effects of AT on children's functioning but more objective than child behavior ratings.[5,10]

The primary aim of this study was to determine whether the eAT group improved more than the WWSC group on select measures of cognitive function. Despite variability in the cognitive tests that best discriminate children with OSAS from healthy controls, OSAS-related weaknesses are most evident on tests of sustained and selective attention, response inhibition, nonverbal reasoning, phonological processing, verbal fluency, and fine motor and visual–motor skills.[6,7,9,14,16–18,30] Findings from nonrandomized trials of AT in children with snoring or OSAS suggest beneficial effects of surgery on attention and nonverbal problem solving.[8,14,19,20] Based on this evidence we hypothesized that the eAT group would improve more across follow-up than the WWSC group on tests of these skills. Within the eAT group we also investigated increases in test scores across follow-up in relation to the degree of improvement in OSAS as measured by overt symptoms and polysomnography. Finally, we explored whether measures of more severe sleep disturbance at baseline were associated with lower baseline test scores.

METHODS

Sample

The rationale and methods of the CHAT trial are detailed in previous reports.[4,28] In brief, between January 2008 and September 2011, 453 participants were recruited by screening children 5.0 to 9.9 years of age referred from sleep programs, pediatric and otolaryngology clinics, and the surrounding communities of 6 academic medical centers. Study procedures were approved by the institutional review boards of each center. Informed consent was obtained from parents or guardians, and assent was obtained from children ≥7 years old. Eligible children were otherwise healthy and had a history of snoring, tonsillar hypertrophy, and polysomnography indicating OSAS without prolonged oxyhemoglobin desaturation (<2% of total sleep time with pulse oxygen saturation <90%) and an obstructive apnea index (apneas per hour of sleep) of 1 to 20 or an obstructive apnea hypopnea index (apneas or hypopneas per hour of sleep) of 2 to 30. Children with extreme obesity (BMI *z* score ≥3) or on psychotropic medications were excluded, including those treated for attention-deficit/hyperactivity disorder.

Procedures and Measures

Before group assignment, participants completed polysomnography and a baseline assessment that included parent ratings of sleep symptoms and child neuropsychological testing.[4] Children were then randomly assigned by the data coordinating center to WWSC (n = 227) or eAT (n = 226). Assignment was stratified by site, age (5–7 or 8–10 years), race (African American or other), and overweight status (BMI age- and gender-adjusted *z* score ≤85% or >85%), with the eAT group receiving surgery within 4 weeks of randomization. All assessments were readministered after 7 months (mean [SD] = 7.1 [0.9]). The follow-up period was chosen as one that would be acceptable to parents and referring physicians while also sufficient to detect post-AT changes in cognitive

test scores.[7,26,31] Measures are listed in Table 1 and included indices of sleep disturbance as assessed by polysomnography, parent ratings, and neuropsychological tests of verbal skills, nonverbal reasoning, attention and executive function, perceptual–motor and visual–spatial skills, and verbal learning and memory (for test descriptions see Supplemental Table 6). Tests were individually administered in 2 fixed sequences counterbalanced across participants by examiners who were uninformed of group assignment.

TABLE 1 Measures

Source and Measure
Polysomnography
Arousal index: number of electrocortical arousals per hour of sleep
Apnea hypopnea index: number of apneas and hypopneas per hour of sleep
Oxygen desaturation index of ≥3% per hour of sleep
Percentage sleep time with end-tidal CO_2 values >50 mm Hg
Percentage sleep time in stage 1 (light) sleep
Percentage sleep time in stage 3 sleep
Percentage sleep time in rapid eye movement sleep
Sleep efficiency: percentage time in sleep during the total recording period
Normalization of OSAS: decrease from baseline to 7-mo follow-up in AHI to <2 events per hour and of obstructive apnea index to <1 event per hour
Parent ratings of sleep disturbance
PSQ-SRBD[32]: proportion of 22 yes/no items endorsed, with higher scores indicating more problems
18-item Obstructive Sleep Apnea assessment tool[33]: range 18–126, with higher scores indicating more negative disease specific quality of life
mESS[34]: range 0–24, with higher scores indicating more sleepiness
Neuropsychological domains and tests
Verbal skills: DAS-II[35] Word Definitions and Verbal Similarities; NEPSY[36] Phonological Processing, Comprehension of Instructions, and Speeded Naming
Nonverbal reasoning: DAS-II Matrices, Sequential and Quantitative Reasoning, Pattern Construction, and Recall of Designs
Attention and executive function: NEPSY Visual Attention, Auditory Attention and Response Set, and Tower; NEPSY-II[37] Inhibition (Naming, Inhibition, and Switching conditions) and Word Generation (Semantic and Initial Letter conditions)
Perceptual–motor and visual–spatial skills: Purdue Pegboard Test[38,39] (Dominant Hand, Non-dominant Hand, and Both Hands conditions); Developmental Test of Visual Motor Integration[40]; NEPSY Arrows
Verbal learning and memory: WRAML2[41] Verbal Learning Test (Learning, Recall, and Recognition conditions)

Standardized scores for age used for all neuropsychological tests, including T-scores for the DAS-II (normative mean [SD] = 50 [10], range 10–90), scaled scores for the NEPSY, NEPSY-II, and WRAML2 (normative mean [SD] = 50 [10], range 1–19), and standard scores for the Developmental Test of Visual Motor Integration (normative mean [SD] = 100 [15], range 45–155). Age standardized scores for the Purdue Pegboard were obtained by regressing the raw scores at baseline on age and sex to estimate expected scores and computing differences in *z* score units between the expected and obtained scores. Higher scores on all neuropsychological tests indicate higher skill levels.

Statistical Analysis

Repeated-measures mixed-effects models were fit to assess group differences in change in age-adjusted standard scores from baseline to the 7-month follow-up. Factors were group (WWSC vs eAT), visit (baseline, follow-up), and the group × visit interaction. Stratification factors and maternal education level were included as covariates. All children with valid test scores were included in the analysis. An intention-to-treat approach was used in the primary analyses, followed by analyses that excluded 20 children (13 WWSC, 7 eAT) who did not receive their assigned treatment (ie, crossovers).

To examine the relationship of changes in the sleep measures to changes in cognitive tests across follow-up for the eAT group, we estimated gains in scores related to practice effects (ie, greater familiarity of children with the tests at follow-up) by using data from the WWSC group. For each test, follow-up scores for these children were regressed on their corresponding baseline scores. The regression equations were then applied to the eAT group to estimate expected follow-up scores. Cognitive change was defined as the standardized difference between the expected and observed scores at follow-up, reflecting the degree to which the follow-up scores differed from those predicted by the baseline scores and practice effects. Subsequent regression models examined changes in the sleep measures as predictors of these change scores, controlling for stratification factors and maternal education. All polysomnography measures except percentage sleep time in rapid eye movement sleep were log transformed to provide more normal distributions. Regression analysis controlling for these same factors was also used to examine associations of baseline neuropsychological test scores for the total sample with baseline sleep measures.

CHAT was designed to detect an effect size of ≥0.32 with 90% power for group differences in the primary outcome of attention and executive function.[28] For the exploratory analyses presented here, corrections were not made for multiple comparisons. We computed effect sizes by using Cohen's *d* for group differences from mixed models and f^2 for regressions, defining small, medium, and large effects, respectively, as 0.2, 0.5, and 0.8 for *d* and 0.02, 0.15, and 0.35 for f^2.[42] We analyzed data by using SAS Proprietary Software 9.3 (TS1M0; SAS Institute, Inc, Cary, NC) and IBM SPSS Statistics Version 23 (IBM SPSS Statistics, IBM Corporation).

RESULTS

Sample Characteristics

Table 2 presents group demographic and sleep characteristics and Table 3

test scores on the neuropsychological battery at baseline and follow-up. Although mean scores at baseline were within the average range relative to normative standards, means for 2 NEPSY 2nd edition (NEPSY-II) Inhibition conditions (Inhibition and Switching) were somewhat reduced relative to other scores (scaled scores = 8, 25th percentile). The WWSC and eAT groups differed significantly in only 1 of the tests at baseline.

Neuropsychological assessments were available at the 7-month follow-up for 203 (89.4%) children in the WWSC group and 196 (86.7%) in the eAT group. Slight differences in this sample compared with that examined in the original study[28] reflect our inclusion of 2 children with partial test data who were excluded from that study because of missing data for the primary outcome. Compared with the children who completed the study, those without follow-up data included proportionally more black than white participants (38 [15%] vs 16 [8%], $P < .05$), had lower sleep efficiency, had lower scores on NEPSY-II Inhibition Switching and NEPSY Arrows, and had higher scores on Purdue Pegboard Both Hands (Ps < .05), but none of these differences varied by group.

TABLE 2 Sample Demographic and Sleep Characteristics at Baseline

Characteristic	WWSC Group	eAT Group
Demographic variables		
Age, y, mean (SD)	7.01 (1.39)	7.06 (1.41)
Male, *n* (%)	118 (52)	101 (45)
Race, *n* (%)		
African American	123 (54)	126 (56)
White	81 (36)	75 (33)
Other	23 (10)	25 (11)
Hispanic ethnicity, *n* (%)	21 (9)	16 (7)
Maternal education less than high school, *n* (%)	64 (32)	62 (32)
BMI *z* score, mean (SD)[a]	0.87 (1.25)	0.87 (1.35)
Overweight, *n* (%)[b]	106 (47)	108 (48)
Polysomnography measures		
Arousal index, median (interquartile range)	7.79 (6.04–10.12)	8.03 (6.31–10.30)
Apnea hypopnea index, median (interquartile range)	4.51 (2.57–8.84)	4.79 (2.78–8.67)
Oxygen desaturation index of ≥3% per hour of sleep, median (interquartile range)	4.71 (2.36–9.48)	4.97 (2.46–10.10)
Percentage sleep time with end-tidal CO_2 values >50 mm Hg, median (interquartile range)*	0.73 (0.28–5.68)	1.80 (0.40–13.93)
Sleep efficiency, median (interquartile range)	92.1 (83.6–96.6)	93.0 (85.5–96.3)
Percentage sleep time in stage 1 (light) sleep, median (interquartile range)	8.0 (6.0–10.7)	7.8 (5.6–10.7)
Percentage sleep time in stage 3 sleep, median (interquartile range)	31.3 (26.5–35.0)	31.4 (26.2–36.8)
Percentage sleep time in rapid eye movement sleep, mean (SD)	18.2 (4.3)	18.6 (4.2)
Behavioral measures of sleep disturbance		
PSQ-SRBD, mean (SD)	0.50 (0.18)	0.49 (0.18)
18-item Obstructive Sleep Apnea assessment tool, mean (SD)	54.12 (18.83)	53.12 (18.33)
mESS, mean (SD)	7.54 (5.15)	7.08 (4.67)

All data are untransformed, with medians (interquartile range) listed for variables with nonnormal distributions.
[a] BMI age- and gender-adjusted *z* score.
[b] Overweight defined as BMI *z* score ≥85%.
* Significant group difference ($P = .035$); all other differences nonsignificant.

Group Differences in Change in Test Scores From Baseline to 7-Month Follow-Up

Results from the intention-to-treat analysis are presented in Table 4. Analysis revealed significant group × visit interactions for Differential Abilities Scales, 2nd edition (DAS-II) Sequential and Quantitative Reasoning and Purdue Pegboard Both Hands. Increases in both scores were larger for the eAT group than for the WWSC group, but effect sizes were small ($d = 0.20$ for both measures). Figure 1 depicts group differences in change on these 2 tests. When crossovers were excluded, group differences with small effect sizes were found for change on Purdue Pegboard Both Hands, unstandardized β (SE) = 0.21 (0.08), $P = .013$, $d = 0.23$, and on NEPSY Visual Attention, β (SE) = 0.65 (0.31), $P = .040$, $d = 0.24$. Additional exploratory analyses failed to reveal evidence that group differences in change varied in relation to weight status, age, or race, although children who were overweight had significantly lower scores than those not overweight on several measures (data not shown). Practice effects were suggested by significant increases in multiple scores across follow-up for both groups.

Associations of Changes in Test Scores With Changes in Sleep Measures for Children in the eAT Group

Regression analysis revealed several associations of improved scores with positive changes in sleep parameters as measured by polysomnography and sleep questionnaires (Table 5). The associations were weak (partial *r*s −0.15 to −0.30) and had small effect sizes ($f^2$0.022–0.088). The associations tended to cluster around select tests and were evident on 2 of the 3 tests on which the eAT group made greater gains across follow-up than the WWSC group (Purdue Pegboard Non-dominant or Both Hands, NEPSY Visual Attention).

TABLE 3 Standard Score Means (SDs) for eAT and WWSC Groups on Neuropsychological Test Battery at Baseline and Follow-up

	WWSC		eAT	
Skill Domain and Test	Baseline (n = 227)	Follow-up (n = 203)	Baseline (n = 226)	Follow-up (n = 196)
Verbal skills				
DAS-II Word Definitions	48.68 (8.15)	49.33 (8.25)	49.78 (9.08)	50.41 (8.35)
DAS-II Verbal Similarities	49.10 (9.09)	50.22 (8.77)	49.46 (7.69)	50.30 (8.72)
NEPSY Phonological Processing[a]	8.49 (3.52)	8.98 (3.14)	9.18 (3.24)	9.39 (3.52)
NEPSY Comprehension of Instructions	10.02 (2.84)	10.18 (2.91)	10.25 (3.00)	10.45 (3.07)
NEPSY Speeded Naming	8.77 (3.30)	9.43 (3.40)	8.99 (3.39)	9.64 (3.11)
Nonverbal reasoning				
DAS-II Matrices	47.07 (7.83)	47.84 (9.69)	47.96 (8.79)	49.88 (8.78)
DAS-II Sequential and Quantitative Reasoning	46.33 (8.67)	46.71 (8.96)	45.93 (8.34)	48.03 (8.67)
DAS-II Pattern Construction	48.54 (7.62)	49.92 (7.54)	48.97 (6.94)	49.76 (6.98)
DAS-II Recall of Designs	48.46 (8.56)	49.67 (8.25)	48.21 (8.57)	49.49 (8.31)
Attention and executive function				
NEPSY Visual Attention	9.93 (2.89)	10.36 (2.88)	9.91 (2.87)	10.96 (3.03)
NEPSY Auditory Attention and Response Set	10.04 (2.68)	10.68 (2.90)	9.99 (2.83)	10.81 (2.62)
NEPSY Tower	10.52 (2.81)	11.28 (2.71)	10.70 (2.95)	11.53 (2.81)
NEPSY-II Inhibition, Naming	8.59 (3.61)	8.90 (3.65)	8.84 (3.54)	9.30 (3.72)
NEPSY-II Inhibition, Inhibition	8.08 (3.43)	8.76 (3.44)	7.83 (3.25)	9.11 (3.42)
NEPSY-II Inhibition, Switching	8.02 (3.02)	8.33 (3.25)	8.01 (3.50)	9.21 (3.81)
NEPSY-II Word Generation, Semantic Condition	10.60 (3.02)	10.77 (3.08)	10.29 (3.05)	10.51 (3.07)
NEPSY-II Word Generation, Initial Letter Condition	8.81 (2.64)	9.24 (3.17)	8.91 (2.64)	9.16 (2.96)
Perceptual–motor and visual–spatial skills				
Purdue Pegboard Dominant Hand	0.03 (1.00)	0.15 (1.05)	−0.03 (0.99)	0.27 (0.96)
Purdue Pegboard Non-Dominant Hand	−0.05 (1.09)	0.15 (1.14)	0.05 (0.90)	0.18 (1.10)
Purdue Pegboard Both Hands	0.03 (0.97)	−0.04 (0.80)	−0.03 (1.02)	0.10 (0.81)
Developmental Test of Visual Motor Integration	95.09 (12.55)	93.91 (10.93)	94.33 (10.06)	93.94 (11.34)
NEPSY Arrows	9.92 (2.77)	10.28 (2.67)	10.31 (2.80)	10.46 (2.72)
Verbal learning and memory				
WRAML2 Verbal Learning	10.04 (2.76)	10.75 (2.77)	10.00 (2.48)	10.71 (2.86)
WRAML2 Verbal Learning Recall	10.26 (2.46)	10.23 (2.65)	10.00 (2.35)	10.22 (2.72)
WRAML2 Verbal Learning Recognition	9.84 (2.87)	10.28 (2.46)	9.89 (3.03)	10.40 (3.01)

[a] Significant group difference (P = .031) at baseline; all other differences nonsignificant. No group differences significant in comparisons limited to children tested at both baseline and follow-up.

Similar associations were found for DAS-II Pattern Construction, NEPSY Auditory Attention and Response Set, NEPSY-II Inhibition Naming Condition, NEPSY-II Word Generation Semantic Condition, and Wide Range Assessment of Memory and Learning, 2nd edition (WRAML2) Verbal Learning. Contrary to expectations, improved scores on Purdue Pegboard Non-dominant Hand were associated with increases in the arousal index, and improved scores on WRAML2 Verbal Learning Recognition were associated with decreased sleep efficiency. Findings were similar when we excluded crossovers.

Associations of Test Scores With Sleep Measures at Baseline

Regressions of baseline test scores on sleep measures for the total sample revealed 3 significant associations. Lower scores on WRAML2 Verbal Learning, DAS-II Word Definitions, and NEPSY-II Word Generation Initial Letter Condition were associated, respectively, with more sleep problems on the Pediatric Sleep Questionnaire Sleep Related Breathing Disorder Scale (PSQ-SRBD), greater sleepiness on the Epworth Sleepiness Scale modified for children (mESS), and higher percentage sleep time in stage 1 sleep. These associations were also weak (partial rs −0.15 to −0.17) with small effect sizes (f^2 0.021–0.025).

DISCUSSION

The current study adds to the previous findings by suggesting small effects of AT on selective cognitive tests. Specifically, children randomly assigned to eAT made more gains than those in the WWSC group on tests of nonverbal reasoning and fine motor skills. In secondary analysis that excluded crossovers, the eAT group also made significantly greater gains on a timed measure of selective attention and visual scanning (NEPSY Visual Attention). Improvements in similar cognitive domains (fine motor coordination, nonverbal reasoning, and attention and impulse regulation) were associated with positive changes in sleep after eAT. The pattern of associations is in line with previous research suggesting that both respiratory disturbances and sleep quality contribute to cognitive functioning in OSAS.[6]

Cognitive weaknesses in children with OSAS are often reported in the domains of attention, executive function, and nonverbal

reasoning.[6,7,14,16–18] Weaknesses in motor dexterity have also been reported in children with snoring or OSAS and adults with OSAS.[24,43,44] The present results offer support for small effects of treatment in these same domains. The effects of sleep disturbance on cognition and behavior have been attributed to sleepiness and to adverse effects of intermittent hypoxia and sleep fragmentation on neural development and brain functioning.[6] Little is known about the effects of these processes on brain development, but frontal, subcortical, hippocampal, and cerebellar regions are especially vulnerable.[7,11,17,44]

Nonrandomized clinical trials of AT in children with OSAS or snoring have documented improved test performance after surgery.[8,14,19,22–26] Several of these studies found greater gains on tests of attention and executive function, visual–motor and spatial skills, nonverbal reasoning, or memory in children receiving AT for OSAS compared with controls, although others have failed to document these effects.[13,16] Post-AT associations between increased attention or nonverbal reasoning scores and improvements in sleep have also been reported.[8,20] However, these studies are limited by their nonrandomized design, which could lead to an overestimation of effects. The current study suggests that cognitive benefits of AT over a 7-month period in children with OSAS without significant hypoxemia are probably small and selective. It is unclear whether such minor effects led to improvements in school performance or other aspects of daily functioning, but some children may have benefited more than others.

Our study failed to find any benefit of AT on tests of language, visual perceptual skills, or global cognitive ability.[6] These negative findings and mean baseline scores that were comparable to normative means for age are in keeping with past evidence for average global cognitive abilities in children with OSAS.[7,12,13] A relative weakness at baseline on NEPSY-II Inhibition is consistent with the vulnerability of children with OSAS to deficits in specific aspects of cognitive ability.[6] However, CHAT was not designed to evaluate the effects of OSAS, and any differences between test means of CHAT participants and normative values may reflect differences in background characteristics between the participants and samples used to establish national standards.

The small effects of AT on cognitive test scores contrast with the more pronounced effects of surgery on child

TABLE 4 Results from Mixed Model Analysis of Group Differences in Test Scores From Baseline to 7-Mo Follow-up

	Within-Group Change, Baseline to Follow-up[a]		Group Difference in Change[b]	
	WWSC	eAT		
Skills Domain and Test	β (SE)	β (SE)	β (SE)	*P*
Verbal Skills				
DAS-II Word Definitions	0.56 (0.48)	0.51 (0.49)	−0.05 (0.69)	.942
DAS-II Verbal Similarities[c]	1.08 (0.51)	0.65 (0.52)	−0.43 (0.73)	.557
NEPSY Phonological Processing	0.43 (0.22)	0.19 (0.23)	−0.24 (0.32)	.443
NEPSY Comprehension of Instructions	0.13 (0.18)	0.06 (0.18)	−0.06 (0.25)	.803
NEPSY Speeded Naming[c]	0.62 (0.20)	0.71 (0.21)	0.08 (0.29)	.773
Nonverbal reasoning				
DAS-II Matrices	0.59 (0.62)	1.67 (0.63)	1.08 (0.88)	.218
DAS-II Sequential and Quantitative Reasoning	0.28 (0.52)	1.82 (0.53)	1.54 (0.74)	.040*
DAS-II Pattern Construction[c]	1.29 (0.44)	0.53 (0.45)	−0.76 (0.62)	.223
DAS-II Recall of Designs[c]	1.12 (0.53)	1.23 (0.54)	0.11 (0.76)	.889
Attention and executive function				
NEPSY Visual Attention	0.42 (0.22)	1.02 (0.23)	0.60 (0.32)	.061
NEPSY Auditory Attention and Response Set[c]	0.64 (0.16)	0.85 (0.17)	0.21 (0.23)	.353
NEPSY Tower[c]	0.74 (0.21)	0.76 (0.22)	0.02 (0.30)	.960
NEPSY-II Inhibition, Naming	0.30 (0.28)	0.43 (0.29)	0.13 (0.40)	.739
NEPSY-II Inhibition, Inhibition[c]	0.66 (0.23)	1.26 (0.24)	0.60 (0.33)	.072
NEPSY-II Inhibition, Switching	0.57 (0.34)	1.19 (0.34)	0.61 (0.48)	.201
NEPSY-II Word Generation, Semantic	0.10 (0.19)	0.17 (0.19)	0.07 (0.27)	.797
NEPSY-II Word Generation, Initial Letter	0.33 (0.27)	0.11 (0.29)	−0.22 (0.39)	.580
Perceptual–motor and visual–spatial skills				
Purdue Pegboard Dominant Hand	0.11 (0.07)	0.31 (0.07)	0.19 (0.10)	.060
Purdue Pegboard Non-Dominant Hand[c]	0.21 (0.07)	0.15 (0.08)	−0.06 (0.11)	.580
Purdue Pegboard Both Hands	−0.03 (0.06)	0.15 (0.06)	0.18 (0.08)	.031*
Developmental Test of Visual Motor Integration	−1.20 (0.76)	−0.64 (0.77)	0.56 (1.08)	.604
NEPSY Arrows	0.28 (0.18)	0.01 (0.18)	−0.27 (0.25)	.280
Verbal learning and memory				
WRAML2 Verbal Learning[c]	0.74 (0.19)	0.72 (0.19)	−0.02 (0.27)	.935
WRAML2 Verbal Learning Recall	−0.05 (0.18)	0.25 (0.18)	0.30 (0.25)	.240
WRAML2 Verbal Learning Recognition[c]	0.45 (0.20)	0.45 (0.20)	0.00 (0.28)	.992

[a] β (SE) for each group is the model estimate of the adjusted mean (SE) change in standard scores (7-mo follow-up minus baseline) for that group.

[b] β (SE) is the model estimate of the adjusted mean (SE) group difference in change in standard scores (eAT group minus WWSC group).

[c] Standard scores increased significantly ($P < .05$) from baseline to 7-mo follow-up for the total sample.

* $P < .05$ for group × visit interaction effect and small effect sizes for group differences in change ($d = 0.20$).

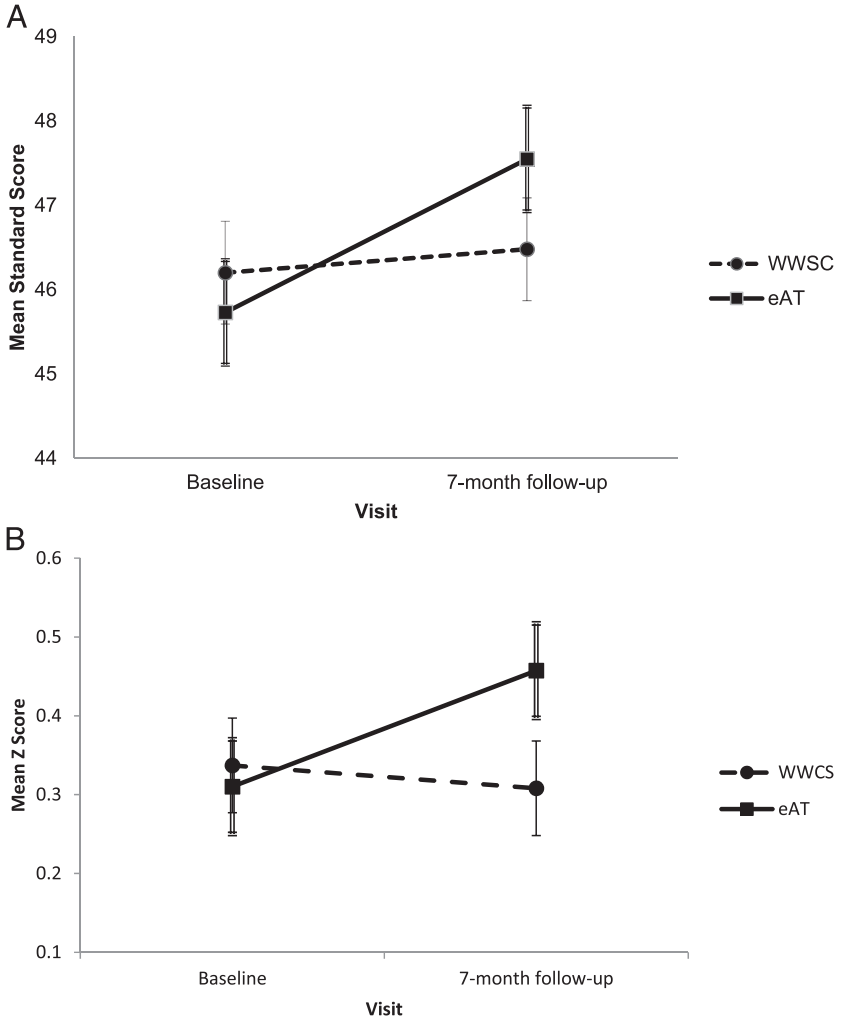

FIGURE 1

Mean standard scores for WWSC and eAT groups on DAS-II Sequential and Quantitative Reasoning test (A) and Purdue Pegboard Both Hands (B) at baseline and 7-month follow-up. Means are estimates from mixed-model analysis. Error bars designate values within 1 SE of the means (single line bars for WWSC group, double lines for eAT group). Results from analysis revealed a significant group × visit interactions (respective *P*s = .040 and .031).

behavior and quality of life.[27,28] One explanation for these small effects is that sleep-related cognitive weaknesses may be less evident on highly structured tests than under "free-living" conditions in which children have to regulate their own behavior according to environmental demands.[45,46] Other possibilities are that the effects of chronic sleep disturbances on brain function are more difficult to reverse than responses to environmental conditions or that longer follow-up is needed to detect more substantial effects of AT on test performance.[11,13,46] The tests used in this study may also be suboptimal for detecting effects of AT; measures placing greater demands on sustained attention and novel problem solving may have been more sensitive to the effects of AT.[11,14,22,26,43,47] Although OSAS measures in the study were those routinely used in clinical settings and scored using rigorous approaches, alternative measures of OSAS or sleep disruption may also provide more sensitive indices of the effects of AT on sleep.[7,8,16,17,20,48]

A secondary aim was to explore associations of baseline test scores with baseline measures of sleep disturbance. Although several past studies failed to identify such associations in samples of children with OSAS or snoring and their controls,[6,8,14,16,21,25,49] other studies report associations of a variety of indices of sleep disturbance with scores on tests of IQ, nonverbal reasoning, vigilance, executive function, and memory.[13,15,17,45,50,51] In agreement with these findings, more symptoms of sleep disruption, greater sleepiness, and a greater percentage of stage 1 sleep were each associated with lower scores on 1 of the cognitive tests. Although the results must be interpreted with caution in view of small effect sizes, they accord with other reports of associations between better sleep and higher neurocognitive functioning.[46]

The design of CHAT conferred several methodological advantages for examining neuropsychological effects of AT and associations of test scores with sleep measures.[3] OSAS was confirmed by standardized polysomnography to ensure uniformity of participant selection and quantification of sleep parameters. Because group assignment was random, potential biases in assessing neuropsychological consequences of AT were minimized. Assessing test score change across follow-up in WWSC group provided an opportunity to take effects of repeat testing into account in assessing the relationship of cognitive changes in the eAT group to changes in the sleep measures. Finally, recruitment from multiple centers yielded a large and diverse sample, and cognitive assessments were comprehensive and administered by examiners naive to group assignment.

This study has several limitations. Effect sizes were small. Moreover, we did not correct for the multiple comparisons, which accords with our exploratory approach[52] but increases

TABLE 5 Findings From Regression Analysis Indicating Significant ($P < .05$) Associations in eAT Group of Changes in Neuropsychological Test Scores With Changes in Sleep Measures

Skill Domain and Test	Sleep Measures Associated With Change	β (SE)	*P*
Nonverbal reasoning			
DAS-II Pattern Construction	Normalization of OSAS	0.40 (0.17)	.023
	Percentage sleep time with end-tidal CO_2 values >50 mm Hg	−0.10 (0.05)	.033
	Sleep efficiency	0.13 (0.06)	.028
Attention and executive function			
NEPSY Visual Attention	PSQ-SRBD	−0.81 (0.41)	.049
NEPSY Auditory Attention and Response Set	Oxygen desaturation index of ≥3% per hour of sleep	−0.15 (0.07)	.037
	Percentage sleep time in rapid eye movement sleep	0.04 (0.01)	.004
NEPSY-II Inhibition, Naming	Percentage sleep time in rapid eye movement sleep	0.03 (0.02)	.036
NEPSY-II Word Generation, Initial Letter	Apnea hypopnea index	−0.38 (0.15)	.015
Perceptual–motor and visual–spatial skills			
Purdue Pegboard Non-dominant Hand	Arousal index	0.39 (0.17)	.021
	Sleep efficiency	0.13 (0.06)	.041
Purdue Pegboard Both Hands	Percentage sleep time with end-tidal CO_2 values >50 mm Hg	−0.16 (0.05)	.002
	Sleep efficiency	0.14 (0.06)	.029
Verbal learning and memory			
WRAML2 Verbal Learning	Oxygen desaturation index of ≥3% per hour of sleep	−0.18 (0.08)	.023
WRAML2 Verbal Learning Recall	mESS	−0.03 (0.02)	.049
WRAML2 Verbal Learning Recognition	Sleep efficiency	−0.17 (0.08)	.031

All *P*s associated with small effect size (Cohen's f^2 0.022–0.088).

the risk of type I error. Findings indicating positive effects of AT on cognition thus require confirmation. Additionally, 2 unanticipated associations of increases in the eAT group's scores across follow-up with negative changes in sleep are difficult to interpret. However, the majority of associations of changes in scores across follow-up with changes in sleep were in the expected direction and were evident for 2 of the 3 cognitive measures in which the eAT group improved more than the WWSC group. Another limitation is that the sample was restricted to children ≥5 years of age with OSAS without prolonged desaturation who were otherwise healthy.

Additional research is needed to investigate the effects of AT on academic learning and determine whether test performance is more affected for some subsets of children than for others. Study of the cognitive effects of AT in children <5 years of age and in those with more severe desaturation or comorbid conditions is likewise warranted. Another important research goal is to identify the types of cognitive skills most affected by AT. The findings suggest that tests of novel problem solving, attention, and motor dexterity are worthy of consideration in future trials. However, future studies might examine ways to increase test sensitivity by assessing speed of decision-making, lengthening tasks, or imposing greater demands on inhibitory control.

CONCLUSIONS

The findings suggest that, on average, AT confers small positive effects on cognitive test scores in children with OSAS without prolonged desaturation and with overall average cognitive functioning. The results provide impetus for more research on the cognitive and neurobiological effects of AT for pediatric OSAS.[5,10,29,44] The findings are also consistent with previous research suggesting that tests of nonverbal reasoning, attention, and fine motor skills are selectively affected by OSAS and thus more likely to improve after AT.

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ABBREVIATIONS

AT: adenotonsillectomy
CHAT: Childhood Adenotonsillectomy Trial
DAS-II: Differential Abilities Scales, 2nd edition
eAT: early adenotonsillectomy
mESS: Epworth Sleepiness Scale modified for children
NEPSY: A Developmental Neuropsychological Assessment
NEPSY-II: NEPSY 2nd edition
OSAS: obstructive sleep apnea syndrome
PSQ-SRBD: Pediatric Sleep Questionnaire Sleep Related Breathing Disorder Scale
WRAML2: Wide Range Assessment of Memory and Learning, 2nd edition
WWSC: watchful waiting with supportive care

Dr Taylor contributed to the study design, oversight of neurobehavioral data collection, and analysis and interpretation of the data, developed the proposal for this manuscript, and drafted and edited the manuscript; Dr Bowen developed the proposal for this manuscript, participated in analysis and interpretation of the data, and helped draft and edit the manuscript; Drs Beebe, Hodges, Thomas, and Giordani contributed to the study design and proposal for this manuscript, oversight of neurobehavioral data collection, and interpretation of the data and edited the manuscript; Drs Amin, Chervin, Garetz, Rosen, Marcus, and Ellenberg contributed to the study design, oversight of data collection, and interpretation of the data and edited the manuscript; Drs Arens, Katz, Muzumdar, and Paruthi participated in oversight of data collection and interpretation of the data and edited the manuscript; Drs Moore and Morales developed the proposal for this manuscript, participated in analysis and interpretation of the data, and edited the manuscript; Drs Sadhwani and Ware contributed to the proposal for this study, oversight of neurobehavioral data collection, and interpretation of the data and edited the manuscript; Dr Redline designed the study, participated in the interpretation of the data, and edited the manuscript; and all authors approved the final manuscript as submitted.

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FINANCIAL DISCLOSURE: Dr Chervin is named in or has developed patented and copyrighted materials owned by the University of Michigan and designed to assist with assessment or treatment of sleep disorders; these materials include the Pediatric Sleep Questionnaire Sleep-Related Breathing Disorder scale, used in the research reported here. This questionnaire is licensed online by the University of Michigan to appropriate users at no charge and (for electronic use) to Zansors. The other authors have indicated they have no financial relationships relevant to this article to disclose.

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