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Authors

Isaiah, Amal
Teplitzky, Taylor B
Dontu, Pragnya
et al.

Publication Date

2023-04-20

DOI

10.1002/ohn.353

AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

Otolaryngology–Head and Neck Surgery
2023, Vol. 00(00) 1–9

DOI: 10.1002/ohn.353
http://otojournal.org
WILEY

Resting-State Cerebral Hemodynamics is Associated With Problem Behaviors in Pediatric Sleep-Disordered Breathing

Amal Isaiah, MD, PhD[1,2,3], Taylor B. Teplitzky, MD[1], Pragnya Dontu, BS[1], Sumeet Saini, BS[1], Maria Som, BS[1], Kevin D. Pereira, MD, MS[1,2], and Heather Bortfeld, PhD[4]

Abstract

Objective. Untreated sleep-disordered breathing (SDB) is associated with problem behaviors in children. The neurological basis for this relationship is unknown. We used functional near-infrared spectroscopy (fNIRS) to assess the relationship between cerebral hemodynamics of the frontal lobe of the brain and problem behaviors in children with SDB.

Study Design. Cross-sectional.

Setting. Urban tertiary care academic children's hospital and affiliated sleep center.

Methods. We enrolled children with SDB aged 5 to 16 years old referred for polysomnography. We measured fNIRS-derived cerebral hemodynamics within the frontal lobe during polysomnography. We assessed parent-reported problem behaviors using the Behavioral Response Inventory of Executive Function Second Edition (BRIEF-2). We compared the relationships between (i) the instability in cerebral perfusion in the frontal lobe measured fNIRS, (ii) SDB severity using apnea-hypopnea index (AHI), and (iii) BRIEF-2 clinical scales using Pearson correlation (r). A $p < .05$ was considered significant.

Results. A total of 54 children were included. The average age was 7.8 (95% confidence interval, 7.0-8.7) years; 26 (48%) were boys and 25 (46%) were Black. The mean AHI was 9.9 (5.7-14.1). There is a statistically significant inverse relationship between the coefficient of variation of perfusion in the frontal lobe and BRIEF-2 clinical scales (range of $r = 0.24$-0.49, range of $p = .076$ to $<.001$). The correlations between AHI and BRIEF-2 scales were not statistically significant.

Conclusion. These results provide preliminary evidence for fNIRS as a child-friendly biomarker for the assessment of adverse outcomes of SDB.

Keywords

behavior, functional near-infrared spectroscopy, sleep-disordered breathing

Received October 26, 2022; accepted March 31, 2023.

Sleep-disordered breathing (SDB), characterized by recurrent and paroxysmal upper airway obstruction, affects approximately 10% of children.[1] Pediatric SDB is most commonly associated with enlarged tonsils and adenoids, but childhood obesity and craniofacial anomalies are also risk factors.[2] While cardiovascular and metabolic disorders are uncommonly related to untreated SDB,[3] the principal indication for children undergoing early treatment of SDB is a concern for neurobehavioral adverse outcomes such as problem behaviors, inattention, and poor classroom performance.[4-6] These deficits are widely hypothesized to be related to exposure to episodic hypoxia and subsequent structural changes within the prefrontal cortex (PFC), a region of the brain central to attention and executive function.[6-8] Therefore, all clinical guidelines recommend early evaluation and possible treatment of SDB by adenotonsillectomy,[9,10] which results in the improvement or resolution of the condition in most children.[11]

Polysomnography is the only objective standard for assessment of the severity of sleep-related upper airway obstruction in obstructive sleep apnea (OSA).[12] Despite some treatment guidelines that recommend preoperative stratification of every child undergoing adenotonsillectomy using polysomnography, its utilization remains low.[13,14] In addition to the logistical and technical challenges associated with preoperative polysomnography, the lack of

[1]Department of Otorhinolaryngology—Head and Neck Surgery, University of Maryland School of Medicine, Baltimore, Maryland, USA
[2]Department of Pediatrics, University of Maryland School of Medicine, Baltimore, Maryland, USA
[3]Department of Diagnostic Radiology and Nuclear Medicine, University of Maryland School of Medicine, Baltimore, Maryland, USA
[4]Department of Psychological Sciences, University of California, Merced, California, USA

This paper was presented orally at the American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS) Annual Meeting; September 11, 2022; Philadelphia, Pennsylvania.

Corresponding Author:
Amal Isaiah, MD, PhD, Department of Otorhinolaryngology–Head and Neck Surgery, University of Maryland School of Medicine, 16 South Eutaw Street Suite 500, Baltimore, MD 21201, USA.
Email: aisaiah@som.umaryland.edu

correlation between polysomnography measures and neurobehavioral outcomes negatively impacts patient selection and caregiver counseling during shared decision-making. Integrating a physiological measure reflecting SDB-related effects on the brain could mechanistically link SDB severity with its neurobiological impacts and guide response to treatment. To date, however, there is no established biomarker that links SDB to its brain-related outcomes such as behavior. Although a few pilot studies exist for the use of magnetic resonance imaging (MRI) to assess both functional and structural changes in the brain related to SDB, these are focused primarily on older children in whom motion artifacts are observed less frequently compared to young children.[15,16] Furthermore, the assessment of real-time cortical physiology during sleep remains even more challenging.

To address these gaps in knowledge, we used functional near-infrared spectroscopy (fNIRS), an optical tool for noninvasive assessment of concentrations of oxyhemoglobin (HbO) and deoxyhemoglobin (HHb) within superficial layers of the cerebral cortex. A large body of evidence suggests that SDB is associated with cortical exposure to intermittent hypoxia and event-related arousals, which could be quantitatively assessed using fNIRS in adults.[17-20] Exposure to intermittent hypoxia within the frontal lobe may account for deficits in attention and behavioral regulation in children.[6,21] Therefore, we hypothesized that the extent of dispersion in cerebral oxygenation within the frontal lobe as measured by fNIRS correlates with problem behaviors in children with SDB.

Methods

We conducted a prospective study of children with SDB aged 5 to 16 years old referred for polysomnography at Mt Washington Pediatric Hospital, a hospital-affiliated sleep center. The study was approved by the Institutional Review Board of the University of Maryland, Baltimore. Exclusion criteria included obesity, defined as a body mass index adjusted for child's weight and age greater than the 95th percentile according to Centers for Disease Control and Prevention charts,[22] craniofacial dysmorphology, neuromuscular tone abnormalities, developmental delay, significant cardiopulmonary disease, and a diagnosis of attention deficit hyperactivity disorder on pharmacological treatment. Participants were excluded after the recording (i) if the total duration of fNIRS or polysomnography was less than 4 hours, (ii) if the fNIRS signal quality was poor, or (iii) if the signal obtained from less than 50% of the duration of polysomnography.

Problem behaviors in enrolled children were assessed using the Behavior Response Inventory of Executive Function 2 (BRIEF-2; PAR Inc), a well-known, validated scale of executive function in children.[23] The BRIEF-2 comprises 63 test items for the parent and takes approximately 10 minutes to complete. Raw scores are converted to *t* scores following linear transformations. The BRIEF-2 report includes the following clinical scales: Inhibit, Self-Monitor, Shift, Emotional Control, Working Memory, Plan/Organize, Initiate, and Organization of Materials. In addition, 4 overall scores are also provided: cognitive, behavior, and emotional regulation, as well as the Global Executive Composite score. The BRIEF-2 is supported by a large standardization sample matched by demographic characteristics to US Census statistics. In addition, the scores also have high internal consistency, test-retest reliability, validity, and interrater and inter-interviewer reliability.

Enrolled participants underwent polysomnography according to the practice parameters established by the American Academy of Sleep Medicine.[12,24] The principal polysomnographic outcome measure was the apnea-hypopnea index (AHI). An obstructive apnea was recorded following a reduction of airflow recorded by the oronasal thermistor, by at least 90%, despite a normal respiratory effort. Hypopnea was a decrease in airflow of at least 30% for at least 2 breaths with either arousal or a 3% decrease in oxygen saturation. Oxygen saturation (SpO_2) nadir was defined as the lowest hemoglobin oxygen saturation recorded by pulse oximetry. Other recorded variables included sleep stages and their durations, duration of hypoxemia as a proportion of total sleep time (TST), sleep efficiency, latency, and capnography.

fNIRS is an optical method for noninvasive measurement of cerebral hemodynamics, specifically the concentrations of HbO, HHb, and total hemoglobin (tHb) concentrations. The underlying principle of fNIRS is the differential absorption of light at various wavelengths by hemoglobin based on the extent of oxygen binding to hemoglobin.[25] These measurements can be used to determine the amounts of HbO and HHb by the modified Beer-Lambert law:

$$\Delta c = \frac{\Delta \mathrm{OD}_\lambda}{\varepsilon_\lambda \cdot L \cdot \mathrm{DPF}},$$

where Δc represents the change in concentration, $\Delta \mathrm{OD}_\lambda$ represents oxygen-independent optical losses from scattering and absorption in tissue, ε_λ is the extinction coefficient of the chromophores, L is the optode distance, and DPF is the differential pathlength factor. The modified Beer-Lambert law adjusts for the increase of optimal path length through biological tissues that scatter light.[26]

We used Portalite® (Artinis Medical Systems), a portable fNIRS device comprised of 3 dual-wavelength (760 and 850 nm) source light-emitting diodes and 1 detector. The Portalite device was secured to the left forehead, 1 to 2 cm above the left brow, which represents the approximate surface marking of the PFC. Relative measures of HbO, HHb, and tHb concentrations, as well as the absolute measure of oxyhemoglobin (tissue saturation

index, TSI) were recorded using the accompanying OxySoft software (Artinis Medical Systems) at a sampling frequency of 10 Hz.

Continuous variables were described by mean and 95% confidence intervals (CIs), and categorical variables were described by numbers (%). Our primary outcome variable was the extent of fluctuation in the oxyhemoglobin concentration estimated by fNIRS. This fluctuation, also called dispersion, was calculated using the ratio of mean to the standard deviation of 3 signals—HbO, HHb, and tHb across 10-second epochs. We used the coefficient of variation (CV) to measure the extent of instability in cerebral oxygenation within the frontal lobe as a neurological substrate for problem behaviors in children with SDB. The CV, also called relative standard deviation, represents a standardized measure of the ratio of the standard deviation to the mean of a signal.[27,28] We then compared the Pearson correlation coefficient between all fNIRS-derived measures and each of the BRIEF-2 scores, as well as between AHI and BRIEF-2 scores. A $p < .05$ was considered significant. All statistical analysis was performed in R (v4.4, https://cran.r-project.org).

Results

A total of 60 children aged 5 to 16 years old meeting inclusion criteria were enrolled from July 2020 to May 2022. Of the 60 participants, 54 children with acceptable fNIRS signal characteristics were included in the study. The average age of the participants was 7.8 (95% CI, 7.0-8.7) years. In addition, 26 (48%) were male and 25 (48%) were Black. The average AHI and nadir were 9.9 (5.7-14.1) and 89.3% (88.1-90.4), respectively. The baseline patient and polysomnography characteristics are shown in Tables 1 and 2. The CV values for individual hemodynamic parameters were 0.03 (0.03-0.03) for TSI, 0.68 (0.50-0.87) for HbO, 1.23 (0.10-2.34) for tHB, and 1.82 (−0.21 to 3.85) for HHb showing maximum and minimum stability for TSI and HHb values, respectively.

Figure 1 shows bivariate Pearson correlations (r) among all the variables. The effect size is low if the value of r varies around 0.1, medium if r varies around 0.3, and large if r varies more than 0.5.[29] Indices representing hypoxemia (oxygen desaturation index [ODI] and TST with SpO_2 <90%) were associated with greater CV in tHB ($r = 0.45$, $p < .001$), HHb ($r = 0.53$, $p < .001$), and TSI ($r = 0.35$, $p = .009$) but not HbO ($r = 0.01$, $p = .96$). Other positive correlations were also identified between ODI and BRIEF-2 scales. No significant relationships were identified between the CV of fNIRS measures representing tHb, HbO, and HHb and any of the BRIEF clinical scales or overall scores. However, TSI CV demonstrated statistically significant positive correlations with all BRIEF scales.

Figure 2 compares Pearson correlations between TSI CV and BRIEF clinical scales as well as AHI and BRIEF

Table 1. Baseline Characteristics of the Study Population.

Variable	Value
Age, y	7.8 (7.0-8.7)
Sex	
Male	26 (48)
Female	28 (52)
Race	
Black	25 (46)
White	22 (41)
Other	7 (13)
Income	
<$30,000	22 (41)
$30,000-$50,000	11 (20)
>$50,000	21 (39)
Parental education	
High school graduate	49 (91)
Passive smoke exposure	7 (13)
Apnea-hypopnea index	9.9 (5.7-14.1)
Oxygen desaturation index	9.0 (5.7-12.3)
Peak end-tidal carbon dioxide, mmHg	58.4 (55.4-61.5)
Oximetry nadir, %	89.3 (88.1-90.4)
Time with oximetry < 90%, min	0.6 (0.2-1.2)
Wake after sleep onset, min	29.8 (22.1-37.5)
Latency, min	49.8 (32.2-67.3)
Efficiency, %	85.5 (82.5-87.7)
Total sleep time, min	399.6 (389.3-409.9)

Variables include demographic and polysomnographic characteristics. Categorical variables are represented by numbers (%) and continuous variables by means (95% confidence intervals).

Table 2. Results of the Assessment of Problem Behaviors in the Study Population.

BRIEF domain	Mean (95% CI)
Inhibit	53.6 (50.7-56.5)
Self-monitor	51.9 (49.0-54.8)
Behavioral regulation index	53.3 (50.3-56.4)
Shift	54.6 (51.2-57.9)
Emotional control	56.4 (53.4-59.5)
Emotional regulation index	55.6 (52.5-58.7)
Initiate	49.6 (47.1-52.0)
Working memory	53.2 (50.4-56.1)
Plan organize	49.5 (47.0-52.0)
Task monitor	50.1 (47.4-52.7)
Organization of materials	50.5 (48.1-52.9)
Cognitive regulation index	51.8 (48.8-54.7)
General executive composite	53.1 (50.2-56.0)

For executive function assessments, the BRIEF-2 was used. Mean (95% CI) t scores are aggregated by clinical scales and composite domain scores. Abbreviations: BRIEF, Behavior Rating Inventory of Executive Function; CI, confidence interval.

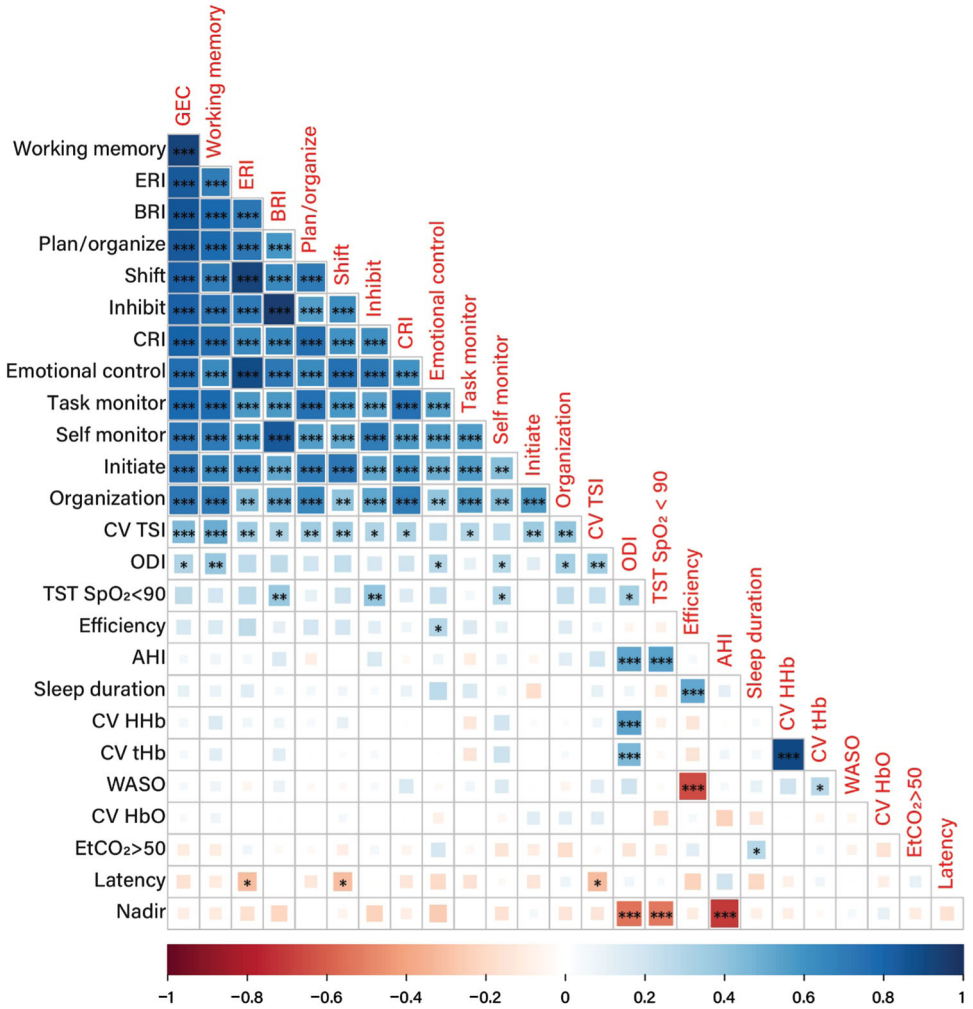

Figure 1. Relationships among polysomnographic, behavior, and functional near-infrared spectroscopy variables. Bivariate correlations between variables along the vertical (black) and the diagonal (red) are shown by the corresponding Pearson *r*. BRI, behavioral regulation index; CV, coefficient of variation, CRI, cognitive regulation index; ERI, emotional regulation index; $EtCO_2$, end-tidal carbon dioxide; GEC, general executive composite; HbO, oxyhemoglobin; HHb, deoxyhemoglobin; ODI, oxygen desaturation index; tHb, total hemoglobin; TSI, tissue saturation index; TST, total sleep time; WASO, wake after sleep onset.

clinical scales. The strongest association was identified between TSI CV and working memory ($r = 0.49$, $p < .001$). Discernible associations were also observed between TSI CV and BRIEF-2 domain scores (Figure 3).

Discussion

The results from this study demonstrated statistically significant correlations between instability in frontal lobe cerebral hemodynamics measured by fNIRS and parent-reported problem behaviors in children with SDB with small to medium effect sizes. On the contrary, none of the correlations between SDB severity measured by AHI and problem behaviors were statistically significant. The results from this study support the use of fNIRS-based frontal lobe cerebral hemodynamics as a potential biomarker for the downstream impacts of SDB and to monitor response to treatment.

Few studies have demonstrated anatomic and functional brain changes in children with SDB. These changes include gray matter loss and cortical thinning in the frontal, parietal, and temporal lobes.[15,30,31] A larger study found cortical thinning in children with SDB among a large sample (n = 12,000) of children enrolled in the Adolescent Brain Cognitive Development study.[6] This study also demonstrated that SDB symptoms and problem behaviors are also accompanied by structural changes within the frontal lobe of the brain, specifically within the PFC, a brain region central to behavioral regulation.[32] However, SDB symptoms in this study were solely parent-reported. Studies using diffusion MRI demonstrated increased diffusivity within the frontal lobe, although in a small sample of children.[33] Functional MRI studies demonstrate decreased spontaneous activity within the left angular gyrus, the frontal gyrus, the lingual gyrus, and the precuneus,[16] while others

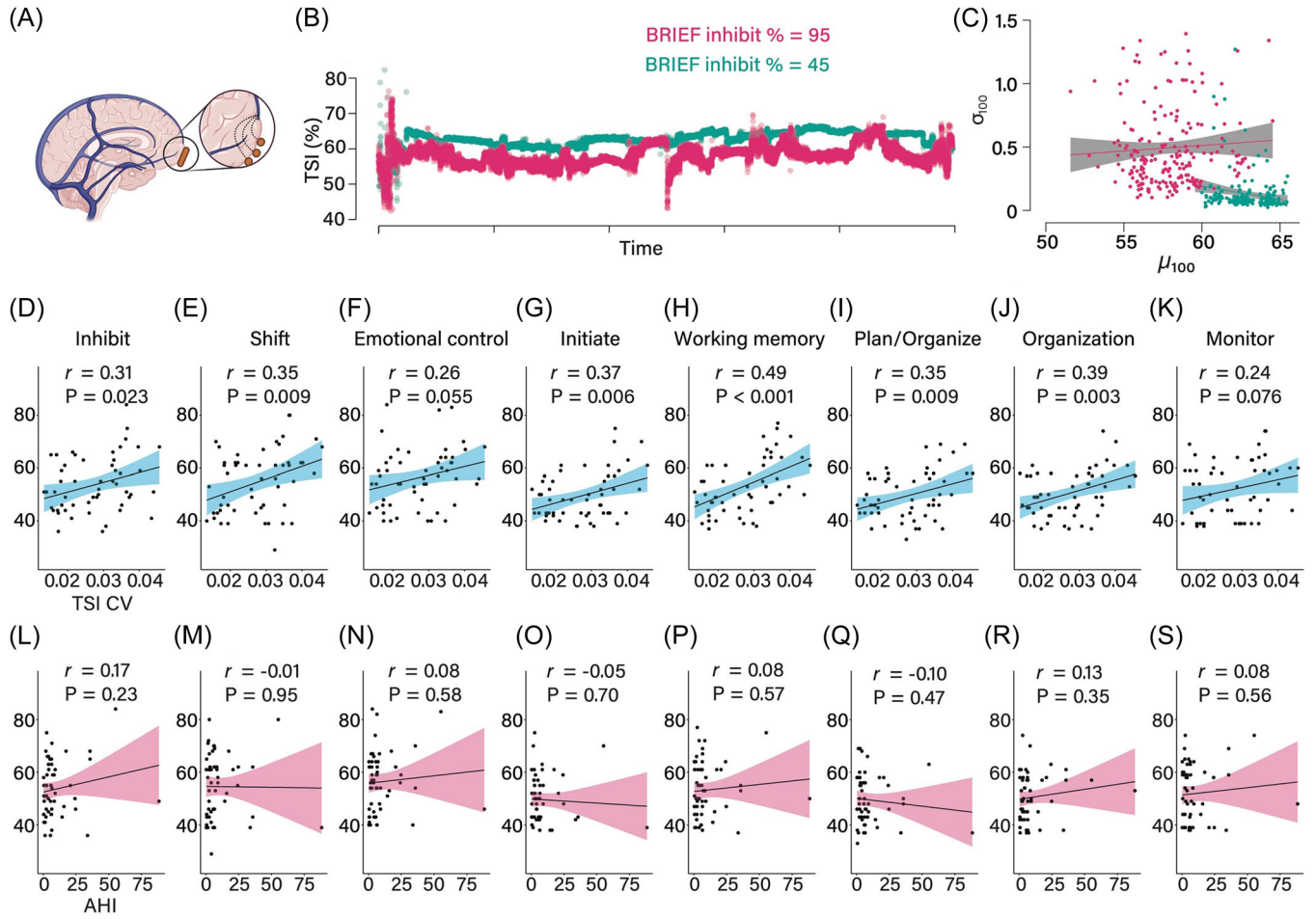

Figure 2. Association between cerebral oxygenation and behavior clinical scales in pediatric sleep-disordered breathing. (A-C) fNIRS signals vary with behavior. (D-K) BRIEF clinical scales versus TSI CV, and (L-S) BRIEF clinical scales versus apnea-hypopnea index (AHI). BRIEF, Behavioral Response Inventory of Executive Function; CV, coefficient of variation; fNIRS, functional near-infrared spectroscopy; TSI, tissue saturation index.

demonstrate compensatory recruitment of areas, such as the anterior cingulate cortex so that children with SDB could function at the same level as children without SDB.[34] The principal drawback of these studies utilizing MRI is that they either have very small sample sizes or comprise children who are older and therefore less likely to generate motion artifacts that degrade MRI signal quality.

Given these bottlenecks associated with the process of imaging brain outcomes of pediatric SDB, many non-invasive techniques to assess cerebral hemodynamics have been investigated. For example, Hill et al[35] identified higher blood flow velocities within the middle cerebral arteries in preschool children with SDB using a pulsed Doppler. They observed an association between these altered cerebral hemodynamics and cognitive impairments, as well as problem behaviors. Furthermore, a follow-up study in the same children showed that neurobehavioral improvements following adenotonsillectomy in children with SDB were accompanied by the normalization of the abnormal cerebral hemodynamics.[36] Other studies, for example, by Spooner et al[37] replicated these findings related to altered hemodynamics thus establishing a novel substrate for characterizing adverse neurobehavioral outcomes in children with SDB.

Perturbations in fNIRS-derived hemodynamic signals in SDB are thought to be the result of complex oxygen supply-demand interactions within the brain. Circulatory disturbances, supraphysiological changes in sleep stages, and arousals may result in greater fluctuation in cerebral hemodynamics. These changes are thought to specifically impact the PFC given the previous evidence showing structural changes within the frontal cortex in children with SDB. Khadra et al[38] used cerebral fNIRS to understand why children with SDB have cognitive deficits independent of AHI. They demonstrated that children with SDB have higher mean systemic arterial pressure, which mitigates the potential drops in regional oxygen saturation levels associated with arousals. Children without this compensatory mechanism may be exposed to greater and more frequent drops in regional cerebral oxygenation. These findings mirror the changes in cerebral oxygenation in response to apneas and hypopneas identified in infants.[39-41] Tamanyan et al[42] studied a

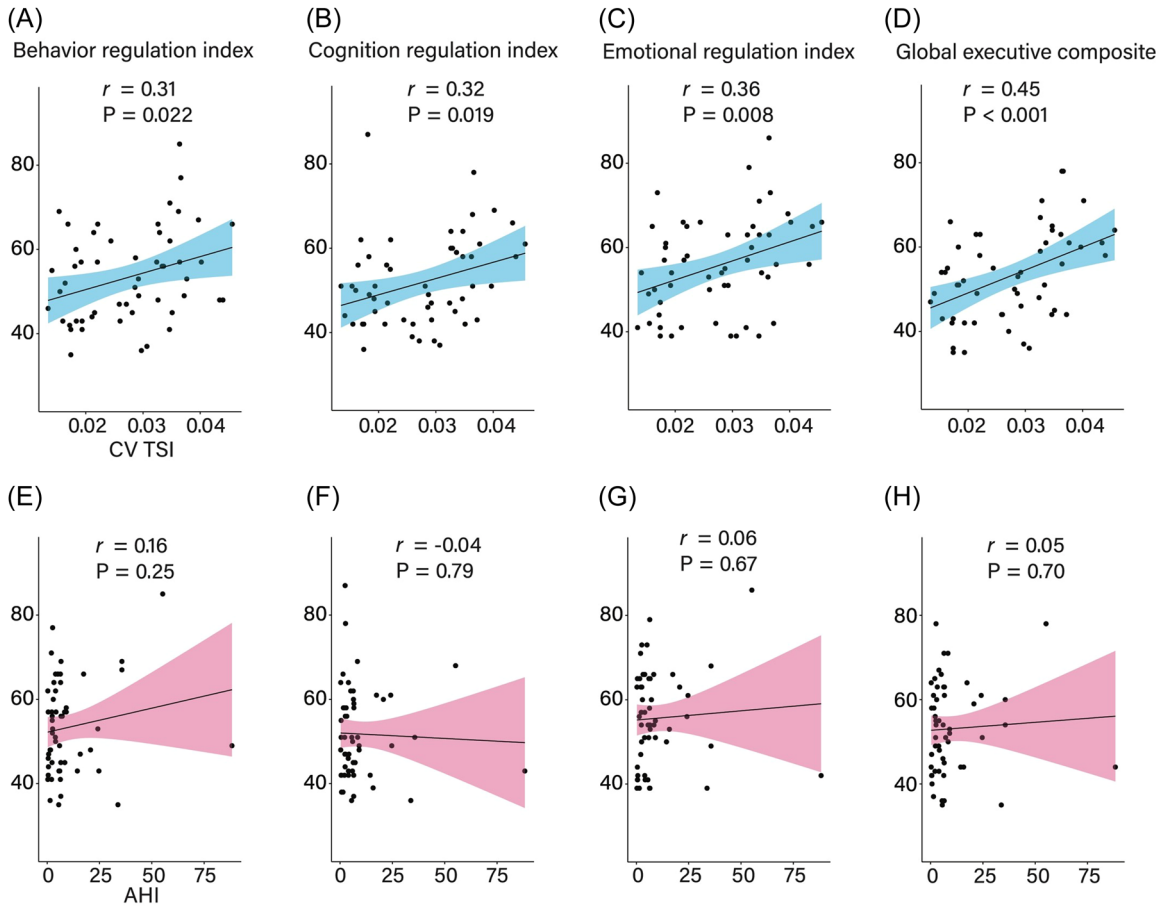

Figure 3. Association between cerebral oxygenation and behavior domain scores in pediatric sleep-disordered breathing. (A-D) BRIEF domain scores versus TSI CV, and (E-H) BRIEF domain scores versus apnea-hypopnea index (AHI). BRIEF, Behavioral Response Inventory of Executive Function; CV, coefficient of variation; TSI, tissue saturation index.

large sample of children (n = 159) grouped into SDB and control groups. They identified lower cerebral oxygenation in the older group of children (7-12 years) with SDB compared to the control cohort. Problem behaviors assessed in this study were paradoxically associated with higher regional cerebral oxygen levels but only among older children. The authors clarified that the behavioral and cognitive characteristics of children enrolled in the study were within the normative range and therefore the clinical relevance of these findings appears to be limited.

Despite most studies concluding that fNIRS recordings tend to be abnormal in children with SDB, fNIRS-derived cerebral oxygenation parameters have not been able to explain the higher prevalence of problem behaviors in children with SDB despite the promising aspects of this method. A major advance was a study by Walter et al[43] that helped characterize adverse neurobehavioral outcomes of SDB better by examining the link between impaired autonomic control and cerebral hemodynamics. The authors demonstrated that SDB disrupts the normal maturation of the autonomic control of heart rate and the association between heart rate variability and cerebral oxygenation exhibited by nonsnoring controls. Therefore, children with SDB are more likely to have impaired cerebral autoregulation, which normally maintains consistent oxygenation levels within the brain. Given that stable hemodynamic patterns are integral to restorative sleep, memory consolidation, and other facets of brain function such as attention,[44] increased fluctuation of cerebral oxygenation may be a potential biomarker of adverse behavioral outcomes observed in the current study. The dispersions of HbO, HHb, and tHb values were not associated with problem behaviors in the current study. As autoregulation primarily involves changes in total cerebral blood volume and velocity, it is unsurprising that the principal goal of cerebrovascular circulatory dynamics is the preservation of absolute tissue concentration of oxygen as measured by TSI. Lastly, it is also not surprising that AHI is not associated with problem behaviors in the current study replicating previous findings in the domain.[5,45] However, polysomnographic indices representing hypoxemia (ODI and TST with SpO_2 <90%) were associated with both CV TSI as well as some of the BRIEF scale scores potentially highlighting the upstream source of changes in cerebral hemodynamics. These findings underscore some of the previous findings that illustrate the role of intermittent hypoxia in the adverse outcomes of SDB in children[46,47]

and emphasize the need to incorporate ODI or other indicators of hypoxia in the polysomnographic classification of SDB severity.[48]

Strengths of the current study include the use of high-frequency sampling that provides a better assessment of real-time changes in cerebral hemodynamics, filtering techniques that mitigate contamination by hemodynamic signals originating from the skin and meninges, and the use of concurrent polysomnography. Weaknesses include the nonstratification by sleep staging, the relatively greater severity of SDB in children enrolled, as well as the noninclusion of control children without SDB. The age range of children in the current study (5-16 years) comprises a wide spectrum of developmental maturity specifically involving neural structures such as the PFC that are refined over adolescence.[49] These age-related impacts also extend to the regulation and morphology of upper airway structures, potentially confounding the findings.[50] Future studies should focus on a focused range of ages for isolating changes related to SDB without the confounding impacts related to developmental maturation that occurs over adolescence.

The fNIRS sensor used in the current study is a commercially available device of the size of a postage stamp and therefore suited for integration into conventional polysomnography or use with oximetry-based screening in low-resource settings. The added value of a physiologic measure that quantifies disease-specific morbidity alongside the severity of upper airway obstruction is to facilitate shared decision-making between treating physicians and families. Given the potential for spontaneous resolution of pediatric OSA in some children that works independent of the related outcomes such as behavior and quality of life,[51,52] a disease-related biomarker could provide additional utility for the preoperative workup of eligible children.[53] Although the commercially available fNIRS sensor used in the current study is expensive owing to the inclusion of Bluetooth®, a recording platform, and an analysis suite, further validation may result in declining costs with the scale of demand. A new open-source device (FlexNIRS) has been described recently with a reported cost as low as $50/unit. The authors have emphasized their revolutionary low cost, ease-of-use, smart-phone readiness, accuracy, real-time data quality feedback, and long battery life suitable for low resource settings, especially for medically underserved communities and telehealth applications.[54] Future research directions include the provision of sleep staging to provide a more accurate assessment of SDB-related hemodynamic changes and to identify postoperative changes related to adenotonsillectomy to understand the causal implications of our observations.

Conclusion

In conclusion, fNIRS technology is a non-invasive assessment of neurobehavioral adverse outcomes in children with SDB. We found a statistically significant inverse relationship between CV of TSI in the frontal lobe as measured by fNIRS and problem behaviors measured by BRIEF-2 clinical scales. There were no discernible relationships between SDB severity measured by AHI and problem behaviors. Our results provide preliminary evidence for cerebral autoregulation in the frontal lobe as a putative biomarker for problem behaviors in children with SDB. Future directions include the impact of sleep staging and treatment (eg, adenotonsillectomy) to understand the causal implications of our findings.

Author Contributions

Amal Isaiah, conceptualization, data analysis, and review of the manuscript; **Taylor B. Teplitzky**, data collection, review, and revision of the manuscript; **Pragnya Dontu**, data collection, initial draft; **Sumeet Saini**,analysis, review, and revision of the manuscript; **Maria Som**, data collection, review, and revision of the manuscript; **Kevin D. Pereira**, conceptualization, manuscript revision; **Heather Bortfeld**, development of methodology, data analysis, review, and revision of the manuscript.

Disclosures

Competing interests: None.

Funding source: None.

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