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Regional brain tissue changes and associations with disease severity in children with sleep-disordered breathing FREE

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Abstract

Study Objectives

Children with sleep-disordered breathing (SDB) exhibit behavioral, cognitive, and autonomic deficits, suggestive of neural injury. We assessed whether the tissue alterations resulted from acute or chronic processes, and whether alterations correlated with disease severity.

Methods

Brain tissue integrity was examined with mean diffusivity (MD) (3.0 T scanner) in 20 nonsnoring controls (mean age ± SEM, 12.2 ± 0.6 years; 10 males) and 18 children with SDB (12.3 ± 0.7 years; 11 males). Sleep, cognitive, and behavioral measures were compared between groups following overnight polysomnography using Student's t tests. Whole-brain MD maps were realigned and averaged, normalized, smoothed, and compared between groups using ANCOVA (covariates: age, gender, and socioeconomic status). Partial correlations were calculated between whole-brain smoothed MD maps and obstructive apnea–hypopnea indices (OAHIs).

Results

Age, gender, and sleep variables did not differ between groups. The SDB group showed higher OAHIs, body mass indices, and systolic blood pressure. Significantly reduced MD values (acute changes) appeared in the hippocampus, insula, thalamus, temporal and occipital cortices, and cerebellum, but were increased (chronic damage) in the frontal and prefrontal cortices in the SDB group over controls. Both positive and negative correlations appeared with extent of tissue changes and disease severity. Externalizing and Total Problem Behaviors were significantly higher in children with SDB. Verbal, performance, and total IQ scores trended lower, and behavioral scores trended higher.

Conclusions

Pediatric SDB is accompanied by predominantly acute brain changes in areas that regulate autonomic, cognitive, and mood functions, and chronic changes in frontal cortices essential for behavioral control. Interventions need to be keyed to address acute vs chronic injury.

magnetic resonance imaging, cognition, mood, autonomic, diffusion tensor imaging

Statement of Significance

Sleep-disordered breathing (SDB) is common in children and is accompanied by behavioral, cognitive, and autonomic deficits suggestive of neural injury. Few studies have assessed brain injury in children with SDB, evaluated whether these were acute or chronic, or related changes to behavioral and physiologic deficits. We used diffusion tensor imaging-based mean diffusivity, to determine acute and chronic brain tissue changes. We related brain tissue changes to physiological, cognitive, and behavioral measures following overnight polysomnography for SDB and its associated impairments. SDB was accompanied by predominantly acute changes in areas that regulate autonomic, cognitive, and mood functions. This finding suggests that resolution of the condition might resolve the injury and associated physiological or behavioral issues, but that the chronic changes in frontal cortices mediating behavioral execution may require alternative or more aggressive interventions.

Introduction

Obstructive sleep-disordered breathing (SDB) embodies a spectrum of respiratory severity disturbances during sleep, which range from primary snoring (PS) to obstructive sleep apnea (OSA). Snoring is the hallmark symptom of SDB, and up to 35% of children snore often or always [1]; OSA occurs in up to 6% of the pediatric population [2]. OSA, the successive collapsing of the upper airway during sleep with continued diaphragmatic efforts, leads to recurrent hypoxic events, elevated CO_2 levels, and sleep fragmentation. We previously showed that all severities of SDB, including PS, are accompanied by elevated blood pressure [3], impaired cardiovascular control [4, 5], and behavioral and neurocognitive sequelae in elementary school-aged children [6, 7]. Those behavioral and physiological sequelae presumably develop from neural changes induced by intermittent hypoxia, high CO_2, fragmented sleep, and altered perfusion accompanying SDB [8]. The neurobehavioral and physiological deficits mandate a need to understand whether the neural changes which precipitate such deficits are amenable to intervention. Establishing potential effectiveness of interventions requires determination of whether the alterations are acute or chronic in nature, since acute changes should be more amenable to treatment of the underlying condition than long-term alterations. The objective of this study was to determine the nature of those neural changes.

To determine the nature of brain changes in children with SDB, we reviewed the patterns found in adult participants with OSA, which showed reduced gray matter density in widely dispersed *regional* areas from the frontal cortex to the cerebellum, and included the medulla, as indicated by voxel-based morphometry procedures [9–14]. Although pediatric neuroimaging studies in SDB are scarce, changes in brain metabolites, systemic inflammatory responses, and reductions in gray matter appear [15–17]. Functional magnetic resonance imaging (fMRI) studies suggest that children with OSA had *greater* neuronal recruitment in brain regions associated with cognitive control, conflict monitoring, and attentional allocation [18]. Children with severe OSA, who exhibited impaired attention and visual-fine motor coordination, showed reduced regional gray matter volumes [17, 19].

Voxel-based morphometry and functional MR studies, however, cannot readily evaluate acute vs chronic tissue injury. Diffusion tensor imaging (DTI)–based mean diffusivity (MD) procedures can measure microstructural brain abnormalities that are affected by extra- or intracellular water content and tissue barriers, including cellular and axonal membranes and macromolecules. The procedures indicate whether those changes reflect acute conditions (decreased MD values appear from cell, neuronal, or axonal swelling caused by water movement from extracellular or axonal to intracellular or axonal spaces) or chronic stages (MD values are elevated over normal values due to the presence of vasogenic edema, demyelination, or axonal/neuronal loss). Determination of acute vs chronic states is essential to evaluate the potential means for intervention [20, 21]. Our aim was to assess regional brain tissue integrity, determine whether alterations were acute or chronic, and whether the changes were associated with disease severity in children with SDB compared with age- and gender-matched nonsnoring control participants. We hypothesized that children with SDB would show altered regional MD values in sites that control autonomic, mood, and cognitive functions over controls, and these changes would indicate both transient and long-term effects on tissue, with disease severity significantly contributing to the extent of tissue changes.

Materials and Methods

The Monash Health and Monash University Human Research Ethics Committees granted ethical approval. Written informed consent was obtained from parents and verbal assent from children before study onset. No monetary incentive was provided.

Participants

Clinical participants were recruited from children (aged 8–18 years) attending the Melbourne Children's Sleep Centre for assessment of suspected SDB ($n = 18$). Age-matched nonsnoring children ($n = 20$) were recruited from the community via advertisements in newsletters circulated to

university and hospital staff and the general community. Children with conditions or taking medications known to affect sleep, breathing, or blood pressure were excluded.

Overnight polysomnography

All children underwent overnight polysomnography (PSG) using standard pediatric criteria [22, 23]. A minimum of 4 hr of sleep was required for study inclusion to diagnose SDB severity.

Prior to the PSG study, sex and age were incorporated into height and weight assessment for measures of body mass index (BMI) *z*-score [24]. Blood pressure was measured in triplicate: during quiet wakefulness and sitting upright, using an electronic blood pressure monitor (Dinamap V100, CARESCAPETM, Freiburg, Germany), with an appropriately sized cuff.

Electrophysiological signals were recorded with a commercially available PSG system (E-Series, Compumedics, Melbourne, Australia) using standard pediatric techniques; full details have previously been published [25]. In brief, electroencephalogram (EEG), left and right electrooculogram (EOG), submental electromyogram (EMG), and left and right anterior tibialis muscle EMG and electrocardiogram (ECG) were attached. Thoracic and abdominal breathing movements, transcutaneous carbon dioxide ($TcCO_2$), nasal pressure, oronasal airflow, and oxygen saturation (SpO_2) were collected. Pediatric sleep technologists sleep-staged and scored the PSG studies manually in 30 s epochs according to clinical practice [22, 23].

Sleep parameters recorded and calculated are included as follows: time in bed (TIB; the time from lights out until the end of the study), sleep period time (the amount of time from sleep onset until morning awakening), total sleep time (TST; the sleep period excluding any period of wake), sleep latency (the period from lights out until sleep onset), REM latency (the period from sleep onset to the onset of the first REM period), sleep efficiency (the ratio of TST to TIB), %WASO (wake after sleep onset as a percentage of sleep period time), and percentage of TST in N1, N2, N3, and REM sleep.

The obstructive apnea–hypopnea index (OAHI) was defined as the total number of obstructive apneas, mixed apneas, and obstructive hypopneas per hour of TST. SDB was defined as an OAHI > 1 event/hr and nonsnoring controls all had an OAHI ≤ 1 event/hr and no history or sign of snoring on the overnight PSG.

Behavioral and neurocognitive testing

Within 2 weeks of the PSG study, children underwent a battery of cognitive testing in their own home to assess cognitive functions most at risk of deficits from SDB. The Stanford-Binet Intelligence Scales, Fifth Edition [26] were used to provide an indication of global intellectual ability. The Abbreviated Battery IQ (ABIQ) was used, consisting of a measure of nonverbal reasoning (performance IQ) and vocabulary (verbal IQ). Raw scores were converted into age-scaled standardized scores (M = 10, *SD* = 3) and then summed and converted to a standardized ABIQ score (M = 100, *SD* = 15). The age-scaled standardized scores for each subset were also converted to standardized scores (M = 100, *SD* = 15) for analysis. Lower scores indicate worse performance on these measures.

The Child Behavior Checklist (CBCL) 6–18 (parent report) [27] was used to assess problem behaviors and emotional difficulties. The domain scores of the *Internalizing, Externalizing,* and *Total Problems Scales* were used.

The Behavior Rating Inventory of Executive Function (BRIEF) (parent report) was used to assess behaviors that reflect executive dysfunction [28]. *Behavior Regulation*, *Metacognition*, and the *Global Executive Composite* scores were compared between groups.

Raw scores on both assessments were converted into age-adjusted, normalized T-scores (M = 50, *SD* = 10). Higher scores indicate worse performance on these scales.

Socioeconomic status (SES) was derived from the Australian Bureau of Statistics Index of Relative Socioeconomic Advantage/Disadvantage (SEIFA) 2011 national census data based on postal code [29]. The SEIFA score has a mean of 1000 with a *SD* of 100 and is presented as a raw score, with a higher score being indicative of higher income, education, employment, occupation, and housing. Maternal and paternal education was also assessed as follows: 1 = completed primary school; 2 = completed part secondary education; 3 = completed secondary education; 4 = completed postsecondary training; 5 = completed an undergraduate university degree; and 6 = completed a postgraduate university degree.

Magnetic resonance imaging

Within 1 week of the PSG study, all children underwent magnetic resonance brain imaging (MRI) using a 3.0 T MRI scanner (Siemens, Magnetom

Skyra, Erlangen, Germany). We used foam pads on either side of the head to minimize head motion-related artifacts. High-resolution T1-weighted images were collected with a magnetization prepared rapid acquisition gradient-echo (MPRAGE) pulse sequence (repetition time [TR] = 2200 ms; echo time [TE] = 2.4 ms; inversion time = 900 ms; flip angle [FA] = 9; matrix size = 320 × 320; field of view [FOV] = 230 × 230 mm; slice thickness = 0.9 mm). Proton-density (PD) and T2-weighted images were acquired using a dual-echo turbo spin-echo pulse sequence (TR = 10000 ms; TE1, 2 = 12, 124 ms; FA = 130°; matrix size = 256 × 256; FOV = 230 × 230 mm; slice thickness = 3.5 mm). DTI was performed using single-shot echo-planar imaging with twice-refocused spin-echo pulse sequence (TR = 13000 ms; TE = 87 ms; FA = 90°; bandwidth = 1345 Hz/pixel; matrix size = 128 × 128; FOV = 230 × 230, 128 × 128 mm; slice thickness = 1.7 mm, no interslice gap, diffusion values = 0 and 700 s/mm^2; diffusion gradient directions = 30; separate series = 2).

Data processing and analysis

The statistical parametric mapping package SPM12 (http://www.fil.ion.ucl.ac.uk/spm/), Diffusion Toolkit, MRIcroN [30], and MATLAB-based (http://www.mathworks.com/) custom software were used to process MRI data.

We used high-resolution T1-, PD-, and T2-weighted images of SDB and control participants to examine for any visible serious brain pathology, such as tumors, cysts, or any other lesions. Diffusion and nondiffusion weighted images of all participants were also examined for any head motion–related or imaging artifact before MD calculation.

Calculation of MD maps

The average background noise level from outside the brain tissue was calculated using nondiffusion and diffusion-weighted images, and this threshold was used to remove nonbrain areas from all participants during MD calculations. Diffusion tensors were calculated using diffusion- (b = 700 s/mm^2) and nondiffusion-weighted images (b = 0 s/mm^2) with Diffusion Toolkit software, and principal eigenvalues ($\lambda1$, $\lambda2$, and $\lambda3$) were derived [31, 32]. Using principal eigenvalues, MD maps [MD = ($\lambda1$+$\lambda2$+$\lambda3$)/3] were calculated from each DTI series [31, 33].

Realignment, averaging, normalization, and smoothing of MD maps

Both MD maps and b0 images, derived from each DTI series, were realigned to reduce any potential motion, and averaged. The averaged MD maps were normalized to Montreal Neurological Institute (MNI) common space using normalization information derived from b0 images. For this normalization, averaged b0 images were partitioned into gray matter, white matter, and cerebrospinal fluid (CSF) tissue types, based on a priori-defined distributions of tissue types [34], and the resulting normalization parameters were applied to the corresponding MD maps and gray and white matter tissue probability maps. The normalized MD maps were smoothed using an isotropic Gaussian filter (8 mm kernel). High-resolution T1-weighted images of all participants were normalized to MNI space and averaged to create background images for anatomical identification.

Global brain mask

The normalized gray and white matter probability maps from all participants were averaged. The averaged gray and white matter probability maps were thresholded (white matter probability > 0.3; gray matter probability > 0.3) and combined to obtain a global brain mask. We used the global brain mask to perform statistical analysis within those clusters.

Statistical analysis

SigmaPlot (Version 13, Systat Software, Inc., California, USA) software was used to examine demographic and sleep variables between groups. We used independent samples Student's t-tests to compare the demographic, sleep, behavioral, and neurocognitive variables. Values are presented as mean ± SEM, with significance considered at $p < 0.05$.

The smoothed MD maps were compared voxel-by-voxel across the whole-brain between SDB and control participants using analysis of covariance, with age, gender, and SES included as covariates (SPM12, uncorrected threshold, $p < 0.005$, 10 voxels). The smoothed MD maps were also used to examine significant relationships between regional brain changes and OAHI values in children with SDB with partial correlation procedures (covariates; age, gender, and SES; SPM12, uncorrected threshold, $p < 0.005$, 10 voxels). We used an extended cluster threshold size (10 voxels) to avoid any appearance of unreliable findings showing significant differences between groups [35, 36]. Brain clusters with significant differences between SDB and controls were overlaid onto background images for anatomical identification.

Results

Demographics and overnight PSG variables

Demographic and polysomnographic variables are summarized in Table 1. The two groups did not differ significantly in age or gender. In the control group, 18/20 children were identified as Caucasian, with the remaining two identified as Caucasian/Asian. In the SDB group, 17/18 children were also identified as Caucasian, with one Australian Aboriginal child. BMI, BMI *z*-score, and OAHI were significantly higher in the SDB group, compared with controls. The control children came from a higher SES (1034 ± 9), compared with the children in the SDB group (1002 ± 12, $p < 0.05$). However, although the SES value differences were statistically significant, the differences between groups were within one standard deviation, and thus, not of any clinical relevance. Maternal and paternal completed education levels did not differ between the groups. Systolic and mean blood pressures were significantly higher in the SDB group compared with controls; however, there was no difference between groups for diastolic blood pressure. Sleep period time was longer in the SDB group; however, no differences were observed between groups for TST, sleep latency, REM latency, or sleep efficiency. The SDB group had a higher %N1 sleep, but no differences emerged between groups for WASO, %N2, %N3, %NREM, or %REM sleep.

Table 1.

Demographic, physiological, and sleep characteristics of nonsnoring controls and children with SDB

Variables	Controls (n = 20)	SDB (n = 18)
Mean age (years)	12.2 ± 0.6	12.3 ± 0.7
Gender (F/M)	10 F/10 M	7 F/11 M
Mean BMI (kg/m^2)	19.0 ± 0.7	26.6 ± 2.4**
BMI z-score	0.23 ± 0.17	1.36 ± 0.28***
SES	1034 ± 9	1002 ± 12*
Maternal education level	median 4.5	median 4
Paternal education level	median 3.5	median 4
Systolic blood pressure (mm Hg)	112.6 ± 2.6	120.4 ± 1.8*
Mean blood pressure (mm Hg)	80.2 ± 1.6	84.5 ± 1.2*
Diastolic blood pressure (mm Hg)	64.1 ± 1.6	66.6 ± 1.5
OAHI (events/hr)	0.3 ± 0.1	7.5 ± 1.9***
SpO_2 nadir (%)	92.2 ± 0.8	88.8 ± 1.3*
Arousal Index (events/hr)	9.7 ± 0.7	14.7 ± 1.6**
Sleep period (min)	429 ± 9	456 ± 9*
Total sleep time (min)	392 ± 8	402 ± 12*
Sleep latency (min)	33 ± 6	29 ± 7
Sleep efficiency (%)	85.1 ± 1.6	82.4 ± 1.9
REM latency (min)	140 ± 14	141 ± 13
Wake after sleep onset (%)	8.7 ± 1.2	11.7 ± 1.8
N1 (%)	6.3 ± 0.6	9.3 ± 1.2*
N2 (%)	49.5 ± 1.6	47.8 ± 1.5
N3 (%)	24.1 ± 1.6	24.3 ± 1.2
NREM (%)	79.9 ± 1.2	81.4 ± 0.9
REM (%)	21.1 ± 1.2	18.6 ± 0.9

Values are mean ± SEM.

SDB = sleep-disordered breathing; BMI = body mass index; OAHI = obstructive apnea–hypopnea index; SES = socioeconomic status; REM = rapid eye movement; NREM = nonrapid eye movement.

*p < 0.05; **p < 0.01; ***p < 0.001.

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Behavioral and neurocognitive outcomes

Behavioral and neurocognitive results are presented in Table 2. The SDB group showed trends for lower scores for Verbal IQ (6 points), Performance IQ (8 points), and Full Scale IQ (7 points). These differences did not reach statistical significance, but the trends are in the direction demonstrated by other studies. Children with SDB exhibited significantly more Externalizing and Total Problem Behaviors (p < 0.05 for both).

Internalizing Behaviors trended to higher values, but did not reach statistical significance. Children with SDB also exhibited trends for more deficits on all scales of the BRIEF.

Table 2.

Cognitive and behavior scores of nonsnoring control children and those with SDB

STANFORD-BINET[†]	Controls	SDB
	***n* = 18**	***n* = 14**
Verbal IQ	93 ± 3	87 ± 3
Performance IQ	102 ± 4	94 ± 4
Full-scale IQ	97 ± 3	90 ± 4
CBCL[‡]	*n* = 20	*n* = 16
Internalizing Behaviors	50 ± 2	57 ± 3
Externalizing Behaviors	47 ± 3*	55 ± 3
Total Problem Behaviors	47 ± 2*	57 ± 4
BRIEF[‡]	*n* = 20	*n* = 16
Behavior Regulation	46 ± 3	54 ± 4
Metacognition	50 ± 3	56 ± 4
Global Executive Composite	47 ± 2	55 ± 4

SDB = sleep-disordered breathing; IQ = Intelligence quotient; CBCL = Child Behavior Checklist; BRIEF = Behavior Rating Inventory of Executive Function.

[†]Stanford-Binet expressed as standardized scores (population mean = 100 ± 15).

[‡]CBCL and BRIEF expressed as T-scores (population mean = 50 ± 10).

*$p < 0.05$.

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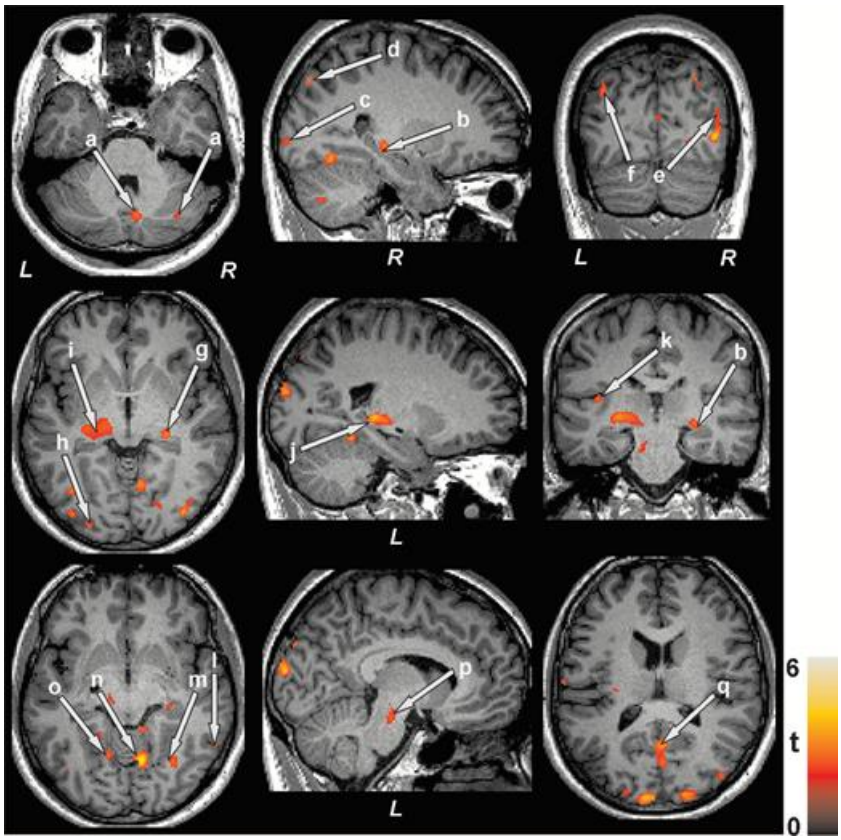
Regional brain MD changes

Several brain areas in children with SDB showed significantly reduced MD values, indicating *acute* injury with axonal and neuronal swelling, compared with control participants. These sites with lower MD values included the bilateral cerebellar vermis, right cerebellar cortex and deep nuclei, bilateral posterior insula, bilateral hippocampus, right cerebral crus, bilateral posterior thalamus, bilateral temporal, and bilateral and midline occipital cortices (Figure 1).

Figure 1.



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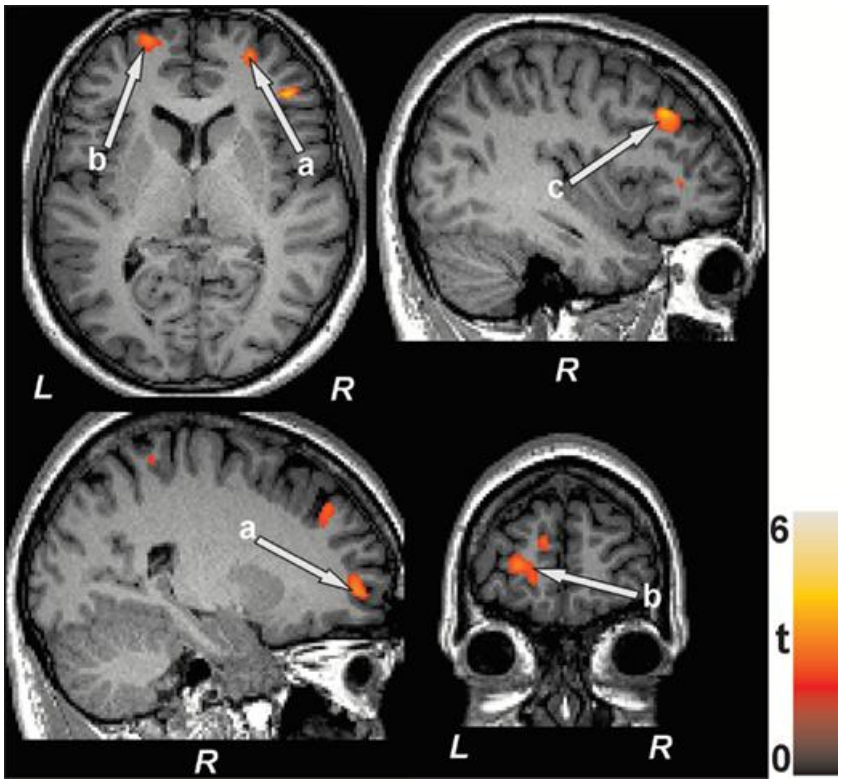
Brain areas showing reduced MD values in children with SDB over nonsnoring control participants. These regions include the cerebellar cortices (a), bilateral hippocampus (b, j), bilateral inferior (c, h), superior (d, f) occipital gyrus, right middle occipital gyrus (e), bilateral posterior thalamus (g, i), posterior insula (k), middle temporal gyrus (l), bilateral lingual gyrus (m, o), cerebellar vermis (n), left midbrain (p), bilateral posterior cingulate (q) (ANCOVA; covariates, age, gender, and SES; $p < 0.005$ uncorrected; extended 10 voxels). All images are in neurological convention (*L = Left; R = Right*). Color scale indicates *t*-statistical values.

A set of brain regions, including the bilateral frontal and prefrontal cortices, showed increased MD values, reflecting greater water mobility due to *chronic* axonal injury in children with SDB over controls (Figure 2).

Figure 2.



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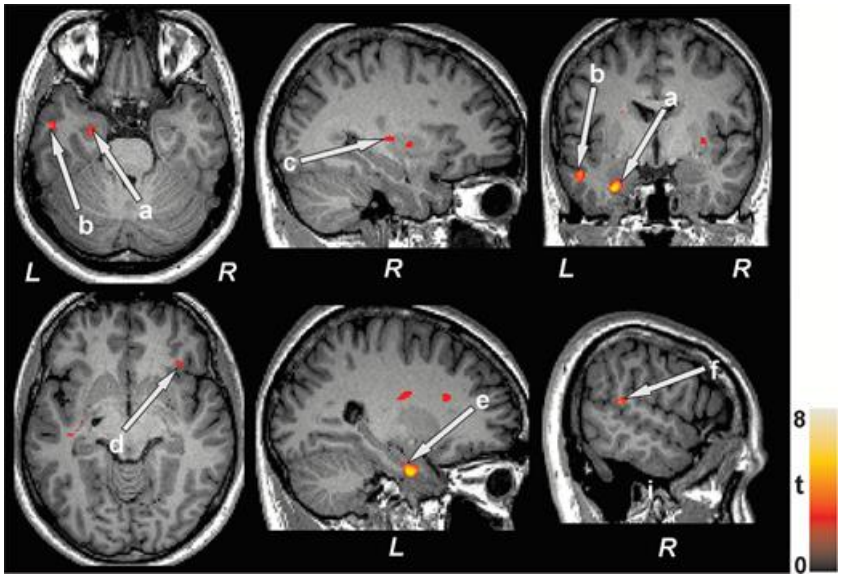
Brain sites with increased MD values in children with SDB compared with nonsnoring controls. Regions with increased MD values in SDB include bilateral prefrontal (a, b) and right middle frontal (c) cortices. Figure conventions are the same as in Figure 1.

Regional brain changes and disease severity

Both positive and negative correlations appeared between regional brain MD and OAHI values in children with SDB. Significant positive correlations appeared in areas which included the left amygdala, left hippocampus, left middle temporal gyrus, right superior temporal gyrus, right anterior insula, right putamen, and right frontal gyrus (Figure 3), and negative associations emerged in multiple sites, including the right cerebellar tonsil, right parahippocampal gyrus, bilateral lingual gyrus, bilateral inferior and middle occipital gyrus, left middle temporal gyrus, and right anterior and left posterior cingulate (Figure 4).

Figure 3.



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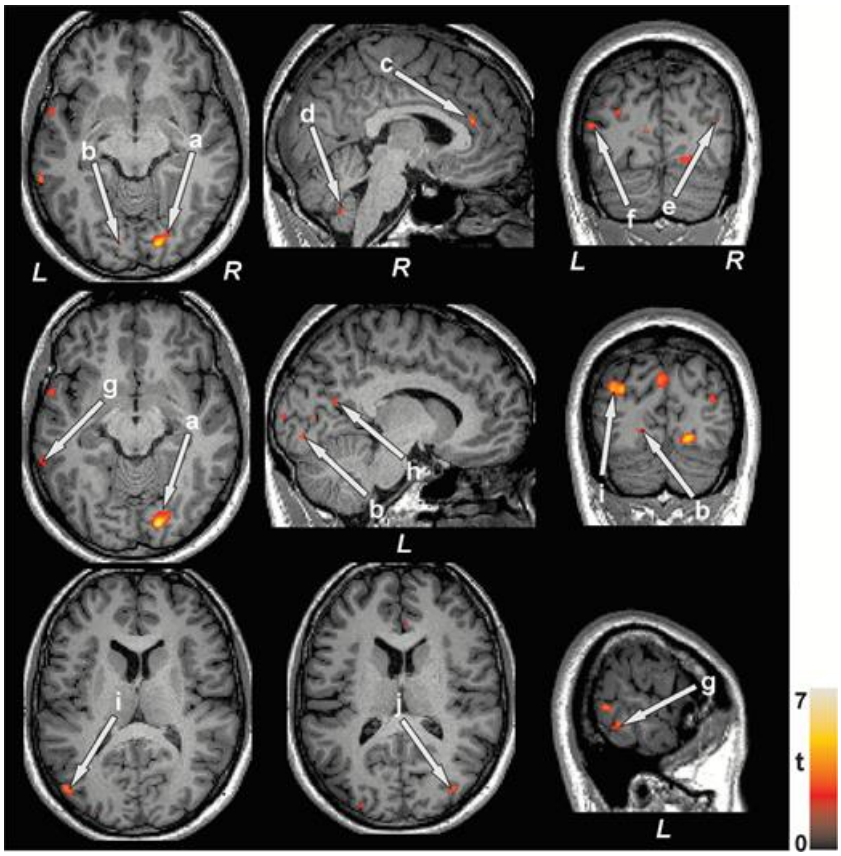
Positive correlations emerged between MD and OAHI values in children with SDB in brain sites including the left amygdala (a), left middle temporal gyrus (b), right putamen (c), right anterior insula (d), left hippocampus (e), and right superior temporal gyrus (f). Figure

conventions are the same as in Figure 1.

Figure 4.



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Negative correlations appeared between MD and OAHI values in children with SDB. Brain sites included bilateral lingual gyrus (a, b), right anterior (c) and left posterior (h) cingulate, right cerebellar tonsil (d), inferior (e, f) and middle (i, j) occipital gyrus, and left middle temporal gyrus (g). Figure conventions are the same as in Figure 1.

Discussion

Several key findings emerge from these studies. Children with SDB show both acute and chronic changes in brain structures which, in the case of acute alterations, suggest a potential for early interventions to reverse regional brain dysfunctions contributing to deficits found in the condition. However, other areas of long-term changes appear—these areas may require more aggressive, sustained, or alternative treatments. Our earlier studies [6, 7] showed multiple cognitive and behavioral deficits in children with SDB; the children with SDB here showed significant indications of behavioral problems, as well as trends for lower IQ scores, likely a consequence of neural changes to frontal regions. Mean and systolic blood pressures were higher in children with SDB, paralleling findings from adults with OSA.

Children with SDB had reduced MD values in the hippocampus, insula, thalamus, temporal, occipital, and cerebellar sites, indicating acute alterations, and increased MD values in the frontal and prefrontal cortices, suggestive of chronic damage. These brain areas are similar to those we previously identified in adults [37]. These brain regions with reduced MD values, especially insular, hippocampal, temporal, and cerebellar sites, are particularly involved in autonomic control, notably cardiovascular and hormonal regulation, as well as respiratory, and cognitive control functions. The cerebellum is particularly involved in dampening of blood pressure changes [38], as well as cognitive influences derived from projections to the frontal cortex [39]. The hippocampus, a key component of the insula-ventral medial prefrontal cortex-hippocampus blood pressure circuitry (for review, see Ref. 40), was also affected. The hippocampus and insula also play key roles in mood, especially depression [41], with the hippocampus particularly important for memory processes (for review, see Ref. 42). These changes reflect acute processes, i.e. they represent recently incurred damage, and as such, may be more amenable to intervention. The cerebellar damage has the potential to alter blood pressure, and with the critical role of the cerebellum in synchronizing upper airway and diaphragmatic action, contributed to the maintenance and even progression of OSA. The mechanisms contributing to the widespread neural injury are many and range from the breakdown in the blood brain barrier, thus far demonstrated in adult OSA [43], but not yet in pediatric SDB, to damage inflicted by intermittent hypoxia in OSA [8].

This study identified both positive and negative correlations between regional brain MD and SDB severity as assessed by the OAHI. Positive correlations were found for the left amygdala, left middle temporal gyrus, right putamen, right anterior insula, left hippocampus, and right superior temporal gyrus. The positive relationships emerged in very limited brain sites, suggesting that chronic brain damage resulted from higher OAHI values with longer durations of SDB. However, widespread negative correlations with OAHI appeared, indicative of acute injuries. There remains the possibility that if OAHI continued, these acute injuries might transition to chronic states.

Negative correlations between OAHI and injury were found in the bilateral lingual gyrus, right anterior and left posterior cingulate, right cerebellar tonsil, inferior and middle occipital gyrus, left middle temporal gyrus, and right para-hippocampal gyrus. The widespread appearance of negative correlations indicates significant potential to exert functional deficits resulting from OAHI, including exacerbations of disordered breathing and blood pressure control.

In a recent study of children aged 7–11 years, 16 with OSA and 9 nonsnoring controls, reduced gray matter volumes were found in the frontal and prefrontal cortices, parietal cortices, temporal lobe, and brainstem regions [17]. However, that study found no associations between brain injury and OSA severity or cognitive ability. In a previous fMRI study, a significant correlation between SDB severity and left amygdala activity in an empathy harm vs neutral actions task was reported in children [18]. The amygdala is involved in the processing of social stimuli and in triggering inspiratory efforts. Single pulse electrical stimulation of the amygdala central nucleus will trigger inspiratory efforts on single pulse-by-pulse basis, a relationship that is lost on entry into sleep [44]. A recent study in children, also using DTI, found decreased MD only in the left dentate gyrus. This alteration was correlated with OSA severity, but not related to neuropsychological measures [45]. The few differences between groups found only in this region may have derived from the control group, which included children with PS and mild OSA (apnea–hypopnea index 0.8 ± 1.1 events/hr), with the OSA group having moderate-to-severe OSA (apnea–hypopnea index 14.8 ± 7.1 events/hr). Previous studies have shown that even PS is associated with adverse cardiovascular, behavioral, and neurocognitive effects [46].

The findings here suggest that increased respiratory disturbances during sleep may derive from impaired descending drives; the emotion processing roles of the amygdala can also influence breathing through descending drives, and injury to the amygdala may alter responses to social stimuli that normally influence breathing. Similarly, SDB severity was also related to deficits in gray matter density, with only those children with severe OSA (OAHI > 5 events/hr) showing reduced gray matter in prefrontal and temporal regions [19].

Children with more severe SDB than those studied here show deficits in gray matter in similar brain regions associated with deficits in visual motor coordination scores [19]. Reduced gray matter volume or density, measured by voxel-based morphometry or MD procedures, appears in frontal, parietal, temporal, hippocampal, and cerebellar regions of adult patients with OSA [9–13]. The damage found here in children was, however, less severe than that reported in adults [9, 12], a finding likely dependent on the age of the study group, and the shorter exposure to repetitive hypoxic events compared with that which occurs in adults. Such short exposure also likely contributes to the proportion of acute vs chronic changes found here.

The prefrontal cortex serves attention and executive function roles. We, and others, have previously shown deficits in these parameters in children with all severities of SDB [6, 7, 46, 47]. The prefrontal cortex may be more vulnerable to the repetitive hypoxia and sleep disruption associated with SDB due to the potential for excitotoxic injury to this area, which receives multiple long-axon projections, placing the region at risk for such injury. The frontal cortex injuries resulting from excitotoxic injury may underlie multiple cognitive deficits with SDB. The neuronal loss may explain why the cognitive deficits associated with SDB are not fully reversible [48], and alternative, or more aggressive interventions are required.

A smaller pediatric OSA study (six controls, five OSA), using MR spectroscopy, showed decreased hippocampal neuronal metabolites *N*-acetyl aspartate (NAA) and choline (Cho) [16], suggestive of hippocampal neuronal injury. The children with severe OSA also showed significantly lower IQ and executive control functions compared with age-, gender-, ethnicity-, and socioeconomically matched control children. A fMRI study showed that both cognitive and empathetic processing were influenced by OSA [18], with children with OSA ($n = 10$) showing greater neural recruitment in the same brain regions as identified in our study which are associated with cognitive control, conflict monitoring, and attention to perform at the same level as control children ($n = 7$). Furthermore, the severity of OSA predicted less sensitivity to harm in the left amygdala. The authors suggested that OSA influences neuronal recruitment across a range of brain activities.

We cannot presume, of course, that the structural brain changes found here result from SDB; it is possible that pre-existing brain damage caused SDB. That aspect needs to be addressed in follow-up studies from earlier stages of life, as well as in longitudinal studies after treatment and resolution of SDB.

Various limitations of this study must be acknowledged. The sample size was small, due to the complexity, cost, and time commitment of the parents and children involved. Similar constraints probably have limited sample sizes in other pediatric studies. Although we endeavored to closely match the control and SDB groups, the children with SDB were more overweight than the control group. This aspect reflects the reality of the referral

population of children in this age group to our sleep laboratory for assessment of SDB. BMI was significantly different in the SDB group compared with controls and was not considered as an additional covariate in the analysis. Since BMI can be a potential confounding factor for abnormal brain changes, this issue should be considered as a limitation. Another limitation was the use of uncorrected threshold ($p < 0.005$). However, we considered clusters only with more than 10 voxels to enhance confidence in our findings. In addition, the use of an adult MNI template over a pediatric template should be considered a minor limitation. However, the normalization performed using SPM12 and verification of those data across all participants against a standard MNI template leaves little room for any error.

Conclusions

Children with SDB showed significantly reduced MD values in hippocampal, insula, thalamic, temporal, occipital, and cerebellar sites, and increased MD values in the frontal and prefrontal cortices over control participants, indicating both acute and chronic tissue changes, respectively. These compromised sites are involved in autonomic, mood, and cognitive regulatory functions that may contribute to deficiencies accompanying the condition. The findings indicate that both short-term and long-lasting processes are operating in children with SDB, probably resulting from a combination of ischemic and hypoxic mechanisms accompanying the syndrome.

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Notes

Conflict of interest statement. None declared.

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