Morbidity of Pediatric OSA

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Four stages of acceptance

1. this is worthless nonsense!
2. this is an interesting, but perverse, point of view
3. this is true, but quite unimportant
4. I always said so…..

John Haldane (1892-1964), English geneticist

Cognitive and Behavioral Consequences

- Snoring and OSA in children are associated with behavioral problems such as hyperactivity, aggressiveness, reduced freedom from distractibility, and learning problems.

Ali et al., 1993, 1994, 1996

Leach et al., 1992

Ferreira et al., 2000

Chervin et al., 2002

- In 297 poorly performing first-graders, the incidence of OSA was 6-9 fold increased.

Gozal D, Pediatrics 1998

Sleep-Disordered Breathing and School Performance in Children

ABSTRACT. *Objective.* To assess the impact of sleep-associated gas exchange abnormalities (SAGEA) on school academic performance in children.

Design. Prospective study.

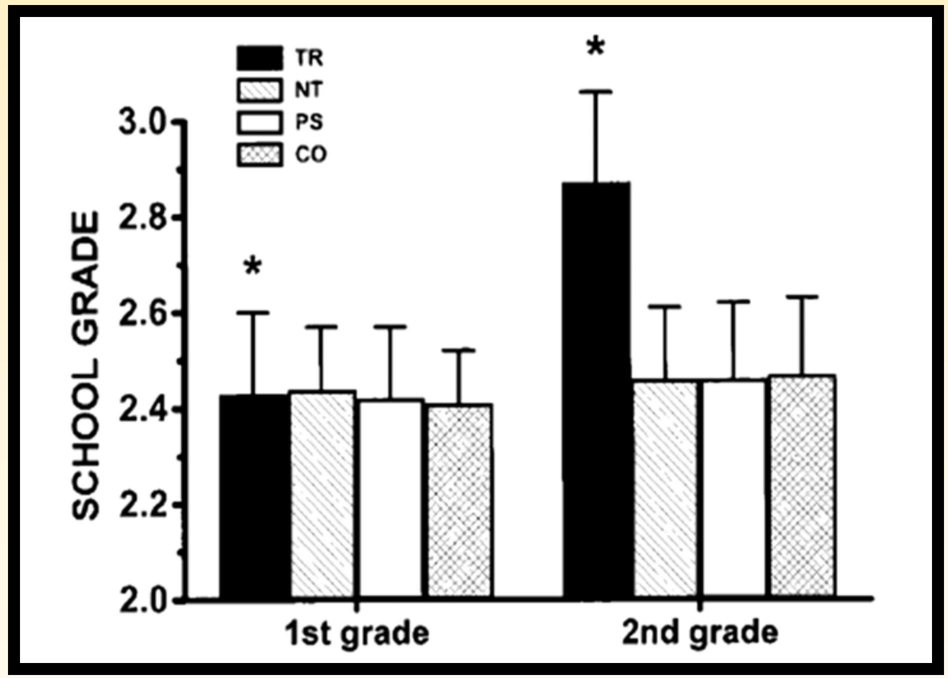
Setting. Urban public elementary schools.

Participants. Two hundred ninety-seven first-grade children whose school performance was in the lowest 10th percentile of their class ranking.

Methods. Children were screened for obstructive sleep apnea syndrome at home using a detailed parental questionnaire and a single night recording of pulse oximetry and transcutaneous partial pressure of carbon dioxide. If SAGEA was diagnosed, parents were encouraged to seek medical intervention for SAGEA. School grades of all participating children for the school year preceding and after the overnight study were obtained.

Results. SAGEA was identified in 54 children (18.1%). Of these, 24 underwent surgical tonsillectomy and adenoidectomy (TR), whereas in the remaining 30 children, parents elected not to seek any therapeutic intervention (NT). Overall mean grades during the second grade increased from 2.43 ± 0.17 (SEM) to 2.87 ± 0.19 in TR, although no significant changes occurred in NT (2.44 ± 0.13 to 2.46 ± 0.15). Similarly, no academic improvements occurred in children without SAGEA.

Conclusions. SAGEA is frequently present in poorly performing first-grade students in whom it adversely affects learning performance. The data suggest that a subset of children with behavioral and learning disabilities could have SAGEA and may benefit from prospective medical evaluation and treatment. *Pediatrics* 1998;



Gozal D, Pediatrics 1998

Coming Back to Kids

Children with lower academic performance in middle school

- More likely to have snored during early childhood .
- More likely to required T&A for snoring .
- OSA associated neurocognitive morbidity may be only partially reversible
- A "learning debt" may develop with OSA during early childhood and hamper subsequent school performance.

Gozal and Pope. Pediatrics.2001

Effect of OSA on Cognitive Performance
Large Community Cohort

- n=1110
- All races and socioeconomic backgrounds
- Snoring and non-snoring
- Ages 5–7 years
- Prospective recruitment from community
- Polysomnography
- Neurocognitive assessments :Intellectual, Attention, Memory, Language and executive function development.
- Subdivided into four severity groups based on AHI
- Comparisons of cognitive function

Hunter et al. Am J Respir Crit Care Med. 2016

NEPSY

(Developmental NEuroPSYchological Assessment)

Attention, Executive function, Language, Memory, Visuospatial planning , Analysis and processing speed

-Children with more severe OSA appeared to have the greatest reduction in executive function.

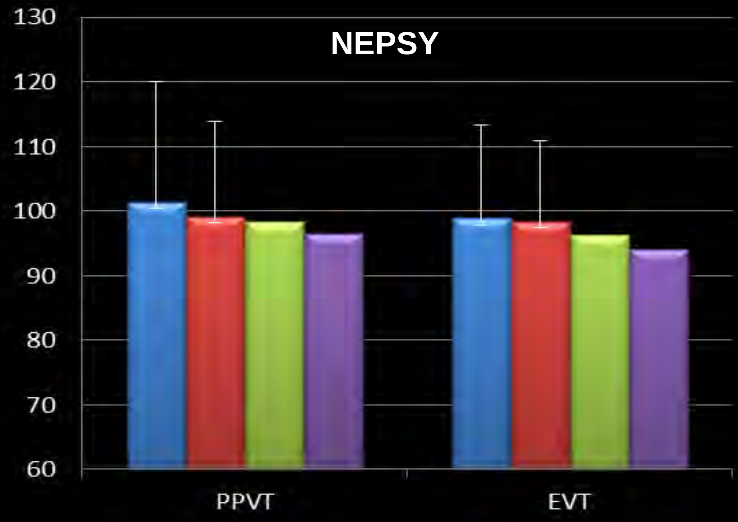
-Attention is more affected in primary snorers compared to non-snoring children

Table 3. Cognitive Function Group Means and SDs

Test	Group 1 (*n* = *90*)	Group 2 (*n* = *431*)	Group 3 (*n* = *348*)	Group 4 (*n* = *141*)
DAS				
Verbal	99.45 (14.20)	98.75 (15.08)	98.02 (15.30)	92.40 (12.49)
Nonverbal	103.26 (15.10)	99.35 (14.23)	99.70 (14.65)	95.63 (12.88)
Global	102.05 (13.66)	99.71 (13.62)	98.79 (14.24)	93.91 (11.93)
NEPSY				
Design Copying	10.83 (3.22)	10.12 (3.00)	9.78 (3.13)	9.14 (3.36)
Phonological Processing	10.08 (3.34)	9.67 (3.79)	9.49 (3.75)	8.66 (3.88)
Tower	11.20 (2.88)	11.32 (3.22)	10.91 (3.34)	9.77 (3.24)
Speed Naming	9.85 (3.05)	9.19 (3.33)	9.04 (3.25)	8.67 (3.20)
Arrows	11.76 (3.02)	10.48 (2.96)	10.35 (2.87)	9.47 (2.61)
Visual Attention	10.69 (2.62)	10.76 (3.00)	10.14 (3.17)	9.80 (3.35)
Comprehension	10.69 (2.59)	10.38 (2.98)	10.03 (2.84)	9.19 (3.05)
PPVT	101.40 (18.58)	99.08 (14.47)	98.47 (14.78)	96.44 (14.87)
EVT	98.88 (14.78)	98.33 (12.63)	96.25 (13.01)	94.01 (13.08)

Definition of abbreviations: DAS = Differential Ability Scales; EVT = Expressive Vocabulary Test; NEPSY = a Developmental Neuropsychological Assessment; PPVT = Peabody Picture Vocabulary Test.

Hunter et al. Am J Respir Crit Care Med. 2016

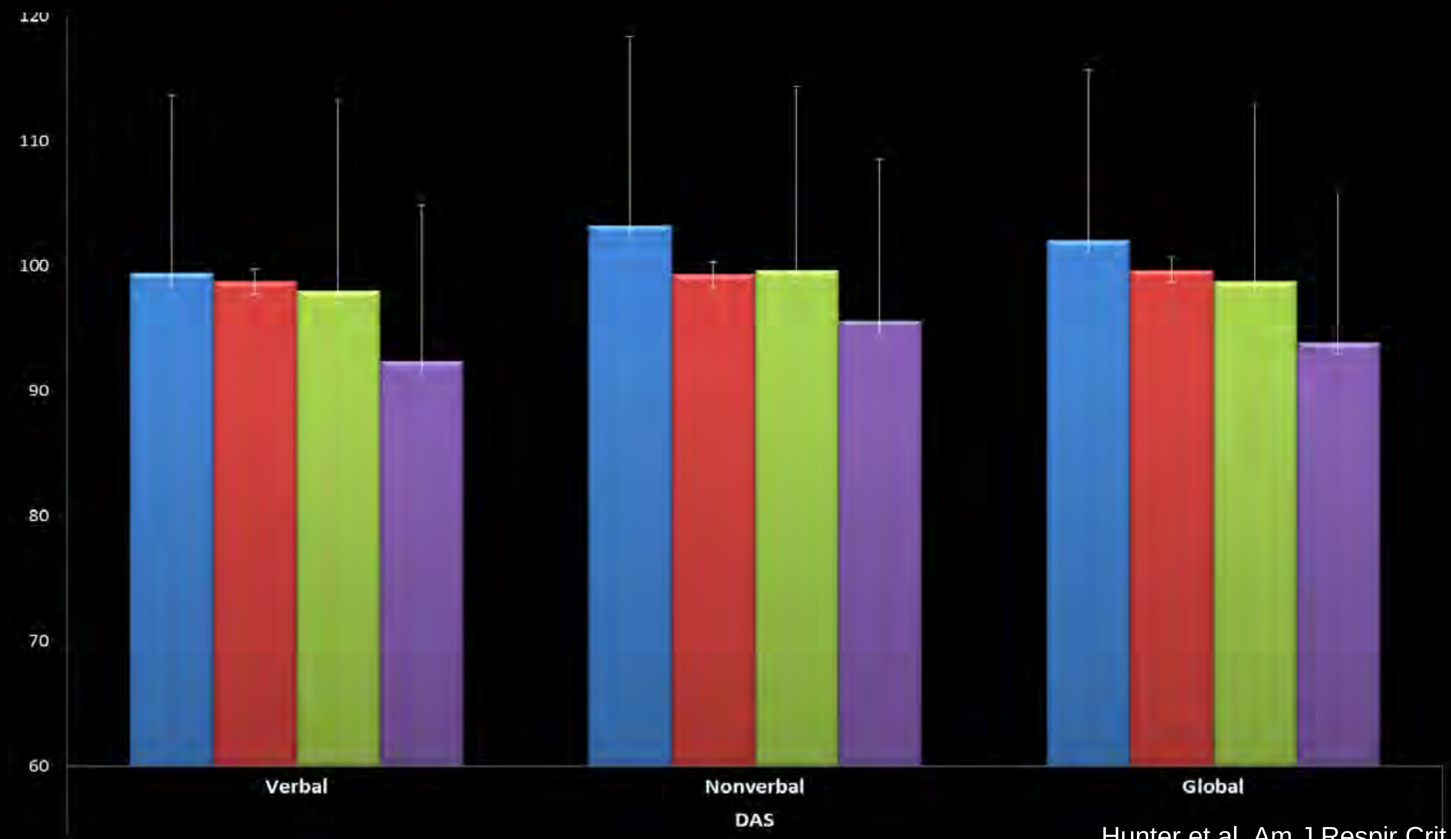


Group 1 n = 90 Non-Snoring Controls

Group 2 n = 431 Primary snoring

Group 3 n = 348 Snore+ 1< AHI <5

Group 4 n = 141 Snore + AHI>5



Hunter et al. Am J Respir Crit Care Med. 2016

AHI was a significant predictor of overall cognitive performance.

Race was a significant predictor of overall cognitive performance (African American children performed more poorly).

Asthma status, BMI, and sex were not significant predictors of overall cognitive performance.

Children who snore and or have OSA perform less efficiently and with less capability across verbal and nonverbal cognitive demands.

ORIGINAL ARTICLE

Effect of Sleep-disordered Breathing Severity on Cognitive Performance Measures in a Large Community Cohort of Young School-aged Children

Scott J. Hunter[1,2], David Gozal[1], Dale L. Smith[3,4], Mona F. Philby[1], Jaeson Kaylegian[2], and Leila Kheirandish-Gozal[1]

Hunter et al. Am J Respir Crit Care Med. 2016

Children with OSA show significant differences compared to normal children

Attention deficits seem to be more dependent on sleep fragmentation.

Behavior and mental processing are more affected by respiratory disturbance and oxygenation.

Effect on Executive Function

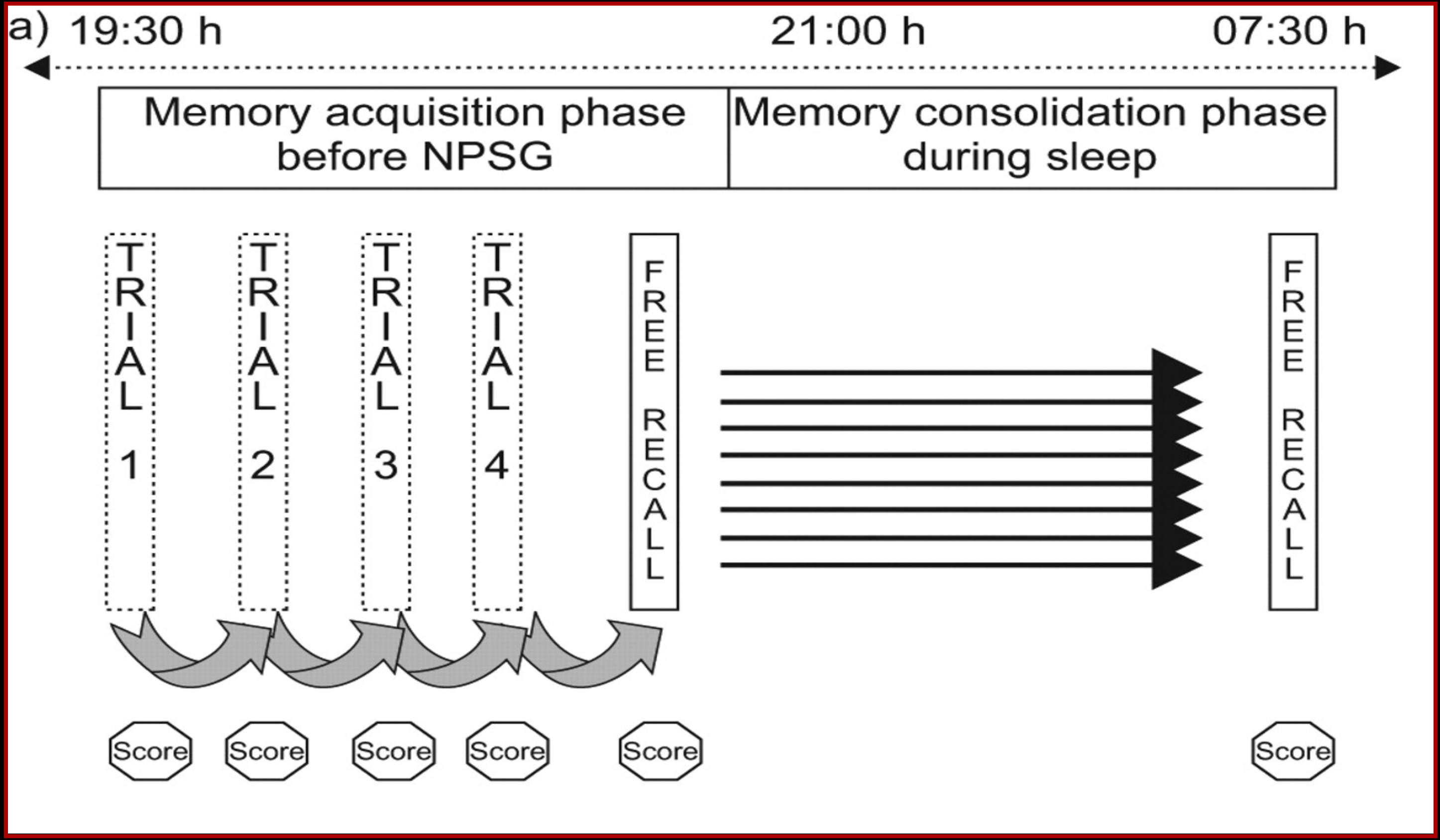
The Tucson Children's Assessment of Sleep Apnea (TuCASA) study:

AHI showed negative correlation with: immediate recall, Full Scale IQ, Performance IQ, and math achievement.

Nocturnal hypoxemia adversely affected nonverbal skills.

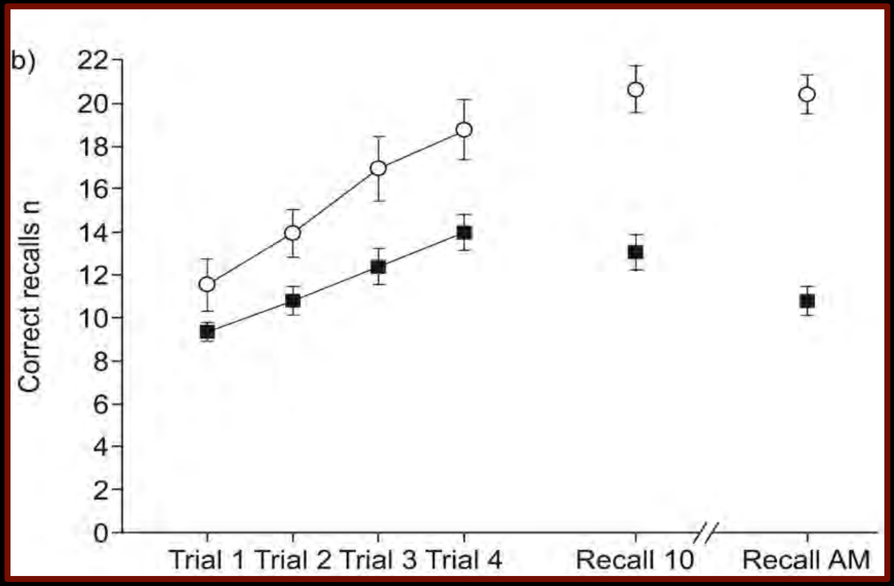
Kaemingk KL et al. J Int Neuropsychol Soc. 2003

Effect of OSA on Declarative Memory



Kheirandish-Gozal L et al. European Respiratory Journal. 2010

Children with OSA compare to the controls of the same age and sex **take longer time and need more learning opportunities** to learn a pictorial-based, short-term and long-term declarative memory test



Kheirandish-Gozal L et al. Eur Respir J. 2010

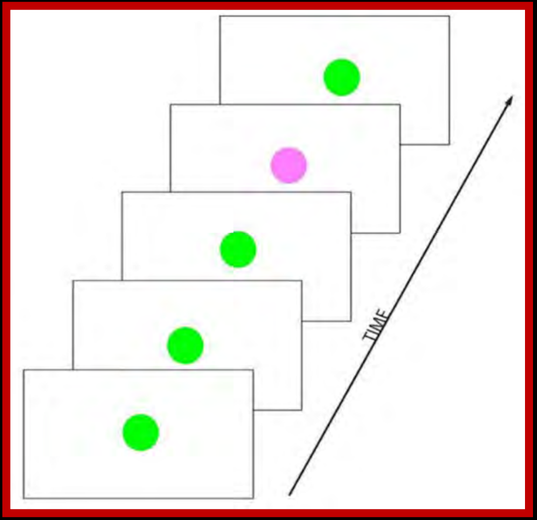
Effect of OSA on Cognitive Function

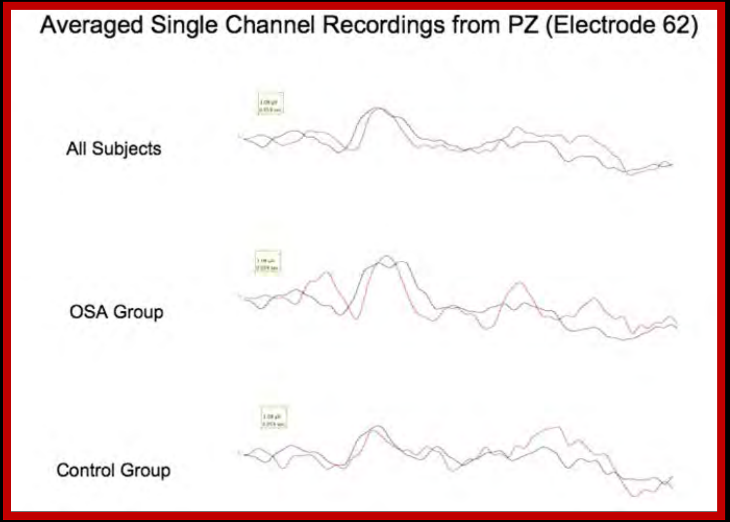
The oddball paradigm is an experimental design used within psychology research.

Presentations of sequences of repetitive stimuli are infrequently interrupted by a deviant stimulus. The reaction of the participant to this "oddball" stimulus is recorded.

An event-related potential (ERP) is the measured brain response that is the direct result of a specific sensory, cognitive, or motor event.

Barnes, Et al. Sleep Medicine. 2012





Effect of OSA on Cognitive Function

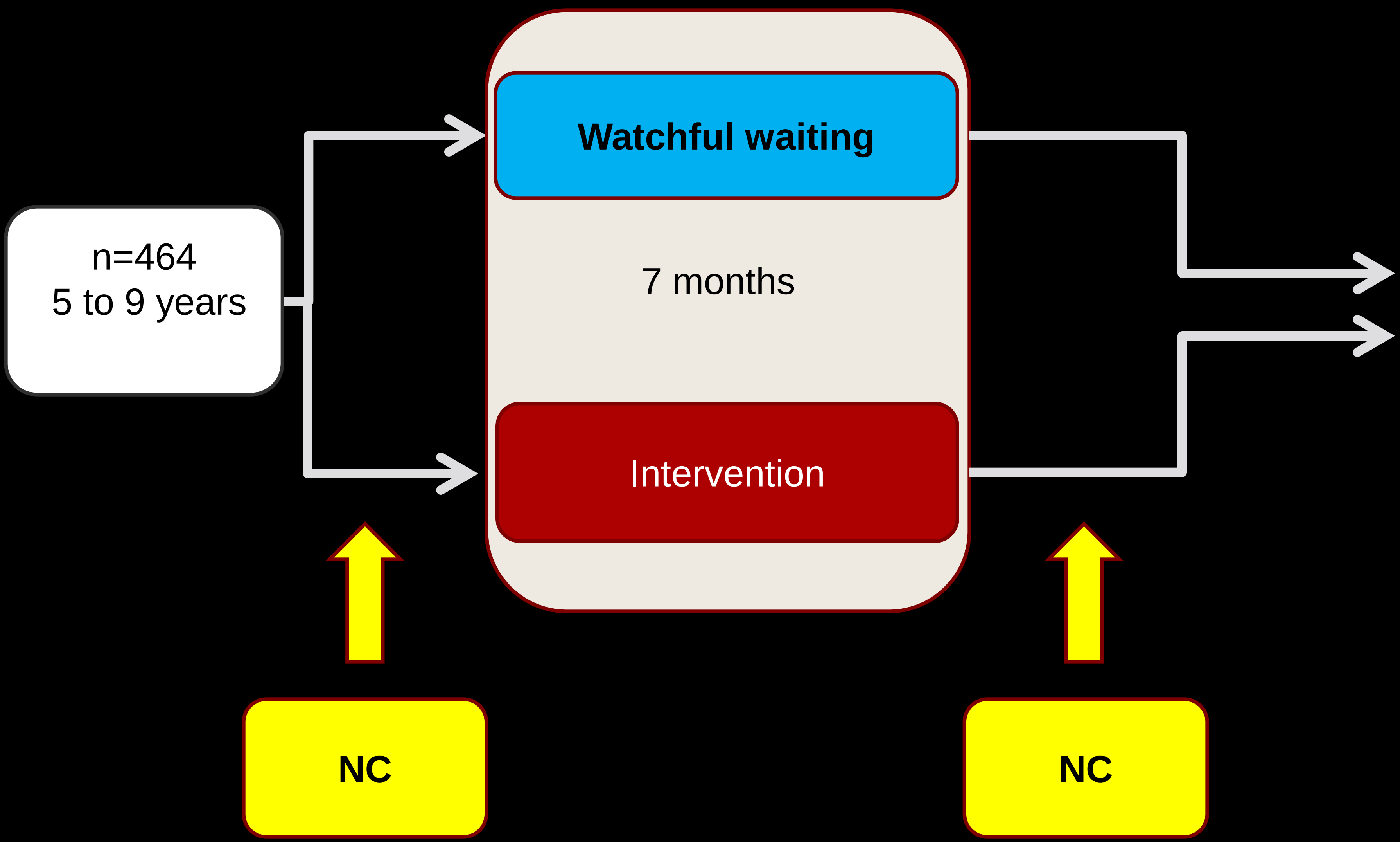
Children with OSA:

Presented with expanded regional recruitment within the prefrontal cortex during performance of an oddball attention task.

Exhibited significantly altered event-related potentials (ERP) patterns of neural activation and impaired neurocognitive performance.

Barnes, Gozal , Molfese . Sleep Medicine. 2012

CHAT Design


n=464
5 to 9 years
Watchful waiting
7 months
Intervention
NC
NC

2013

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Adenotonsillectomy for Childhood Sleep Apnea

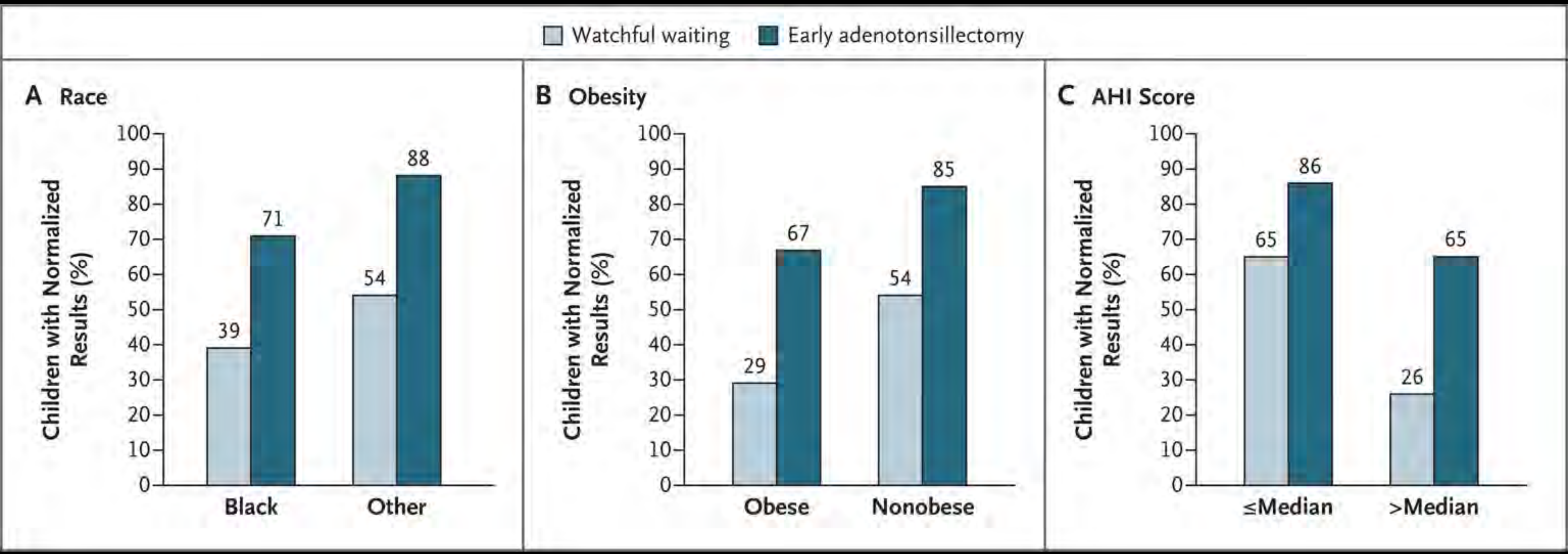
Carole L. Marcus, M.B., B.Ch., Reneé H. Moore, Ph.D., Carol L. Rosen, M.D., Bruno Giordani, Ph.D., Susan L. Garetz, M.D., H. Gerry Taylor, Ph.D., Ron B. Mitchell, M.D., Raouf Amin, M.D., Eliot S. Katz, M.D., Raanan Arens, M.D., Shalini Paruthi, M.D., Hiren Muzumdar, M.D., David Gozal, M.D., Nina Hattiangadi Thomas, Ph.D., Janice Ware, Ph.D., Dean Beebe, Ph.D., Karen Snyder, M.S., Lisa Elden, M.D., Robert C. Sprecher, M.D., Paul Willging, M.D., Dwight Jones, M.D., John P. Bent, M.D., Timothy Hoban, M.D., Ronald D. Chervin, M.D., Susan S. Ellenberg, Ph.D., and Susan Redline, M.D., M.P.H., for the Childhood Adenotonsillectomy Trial (CHAT)

Why “CHAT” study DID NOT show any evidence of improved cognition after treatment?

- Unique randomized controlled trial
- Mild clinical sample with few showing cognitive morbidity on testing
- Restrictions on specific SDB severity limits
- Did not report analyses of the effect of treatment in the subset of children with cognitive deficits
- Taylor et al in a subsequent post-hoc secondary analysis showed improvements in selected NC tasks

Pediatrics 2016

Normalization of Polysomnographic Findings.



Baseline Characteristics of Patients Who Completed the Study.

Table 1. Baseline Characteristics of Patients Who Completed the Study.*

Characteristic	Watchful Waiting (N=203)	Early Adenotonsillectomy (N=194)
Age — yr	6.5±1.4	6.5±1.4
Male sex — no. (%)	106 (52)	89 (46)
Race — no. (%)†		
Black	108 (53)	103 (53)
White	76 (37)	67 (35)
Other	19 (9)	24 (12)
Hispanic ethnicity — no. (%)†	17 (8)	15 (8)
Height — cm	124.7±10.5	125.1±11.2
Height z score	0.6±1.0	0.7±1.0
Weight — kg	30.1±11.7	31.2±13.1
Weight z score	1.0±1.2	1.0±1.3
Weight class — no. (%)‡		
Overweight or obese	94 (46)	93 (48)
Obese	67 (33)	68 (35)
Failure to thrive	3 (1)	4 (2)
Maternal educational level less than high school — no. (%)	64 (32)	62 (32)
Annual household income <$30,000 — no. (%)	82 (40)	73 (38)

* Plus–minus values are means ±SD. There were no significant differences between the study groups. The characteristics of the sample included in the primary outcome analysis were similar to those of the baseline population, except that black children were less likely to complete the study (P=0.04), but this trend was evident in both study groups (Table S1 in the Supplementary Appendix).

† Race reported by caregivers.

‡ Overweight or obese was defined as a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) in the 85th percentile or higher, obese as a BMI in the 95th percentile or higher, and failure to thrive as a BMI in less than the 5th percentile.

Outcome Measures.

Table 2. Outcome Measures.*

Outcome	Normative Mean	Watchful Waiting		Early Adenotonsillectomy		Effect Size†	P Value
		Baseline	Change from Baseline to 7 Mo	Baseline	Change from Baseline to 7 Mo		
Primary outcome							
NEPSY attention and executive-function score‡	100±15	101.1±14.6	5.1±13.4	101.5±15.9	7.1±13.9	0.15	0.16
Secondary outcomes							
Conners' Rating Scale score§	50±10						
Caregiver rating		52.6±11.7	−0.2±9.4	52.5±11.6	−2.9±9.9	0.28	0.01
Teacher rating		55.1±12.8	−1.5±10.7	56.4±14.4	−4.9±12.9	0.29	0.04
BRIEF score¶	50±10						
Caregiver rating		50.1±11.5	0.4±8.8	50.1±11.2	−3.3±8.5	0.28	<0.001
Teacher rating		56.4±11.7	−1.0±11.2	57.2±14.1	−3.1±12.6	0.18	0.22
PSQ-SRBD score‖	0.2±0.1	0.5±0.2	−0.0±0.2	0.5±0.2	−0.3±0.2	1.50	<0.001
PedsQL score**	78±16	76.5±15.7	0.9±13.3	77.3±15.3	5.9±13.6	0.37	<0.001
Apnea–hypopnea index — no. of events/hr††	NA						
Median		4.5	−1.6	4.8	−3.5	0.57	<0.001‡‡
Interquartile range		2.5 to 8.9	−3.7 to 0.5	2.7 to 8.8	−7.1 to −1.8		

* Plus–minus values are means ±SD, and nonnormally distributed data are medians with interquartile ranges. All P values were adjusted for the stratification factors of age (5 to 7 years of age vs. 8 to 9 years of age), race (black vs. other), weight status (overweight or obese vs. nonoverweight), and study site. NA denotes not applicable.

† Effect sizes were calculated with the use of Cohen's d, relating the magnitude of group difference to the standard deviation, and may be interpreted as follows: small, more than 0.20 to 0.49; medium, 0.50 to 0.79; and large, 0.80 or more.

‡ Scores on the attention and executive-function domain of the Developmental Neuropsychological Assessment (NEPSY) range from 50 to 150, with higher scores indicating better functioning. Data are shown for 203 patients in the watchful-waiting group and 194 in the early-adenotonsillectomy group.

§ Scores on the Conners' Parent Rating Scale Revised: Long Version Global Index, comprising the Restless–Impulsive and Emotional Lability factor sets, range from 38 to 90, with higher scores indicating worse functioning.[12] Data are shown for 199 patients in the watchful-waiting group and 193 in the early-adenotonsillectomy group. Scores on the Conners' Teacher Rating Scale Revised (with scores ranging from 40 to 90 and higher scores indicating worse functioning) are shown for 109 patients in the watchful-waiting group and 103 in the early-adenotonsillectomy group.

¶ On the Behavior Rating Inventory of Executive Function (BRIEF) Global Executive Composite section, comprising summary measures of behavioral regulation and metacognition, higher scores indicate worse functioning.[13] Data on the caregiver ratings, with a range of 28 to 101, are shown for 197 patients in the watchful-waiting group and 195 in the early-adenotonsillectomy group. Data on the teacher ratings, with a range from 37 to 131, are shown for 103 patients in the watchful-waiting group and 104 in the early-adenotonsillectomy group.

‖ Scores on the Pediatric Sleep Questionnaire sleep-related breathing disorder scale (PSQ-SRBD) range from 0 to 1, with higher scores indicating greater severity.[14] Data are shown for 202 patients in the watchful-waiting group and 194 in the early-adenotonsillectomy group.

** Scores on the Pediatric Quality of Life Inventory (PedsQL) range from 0 to 100, with higher scores indicating better quality of life.[16,21] Data are shown for 204 patients in the watchful-waiting group and 195 in the early-adenotonsillectomy group.

†† A score of 2 or more on the apnea–hypopnea index indicated the obstructive sleep apnea syndrome. Higher scores indicate more severe obstructive sleep apnea.

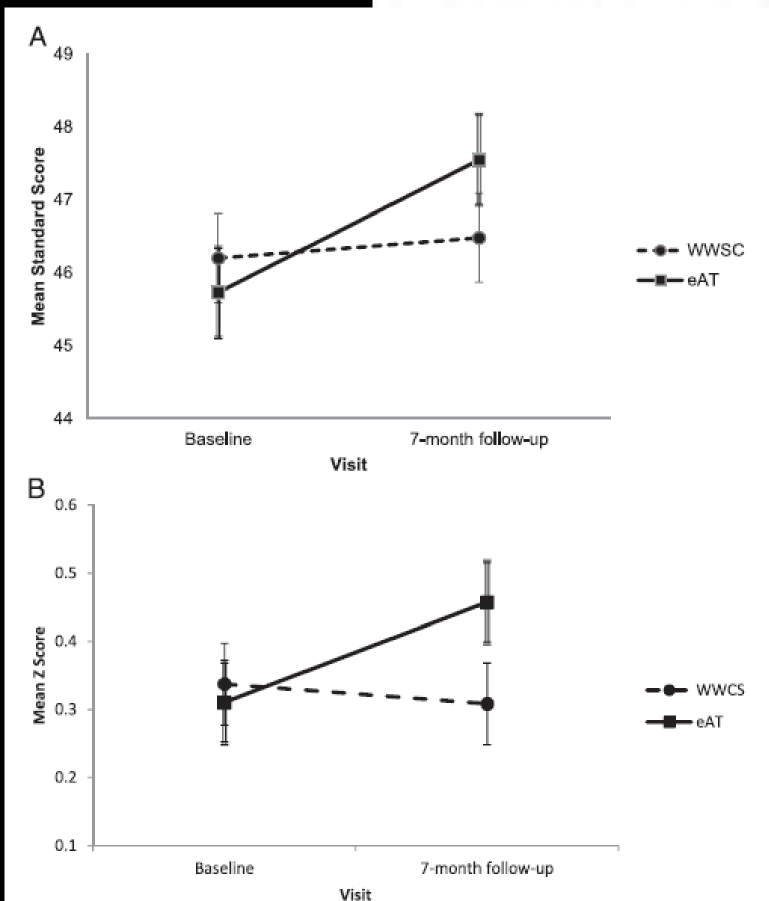
‡‡ Testing was performed on naturally log-transformed variables.

The NEW ENGLAND JOURNAL of MEDICINE

Cognitive Effects of Adenotonsillectomy for Obstructive Sleep Apnea

PEDIATRICS Volume 138, number 2, August 2016:

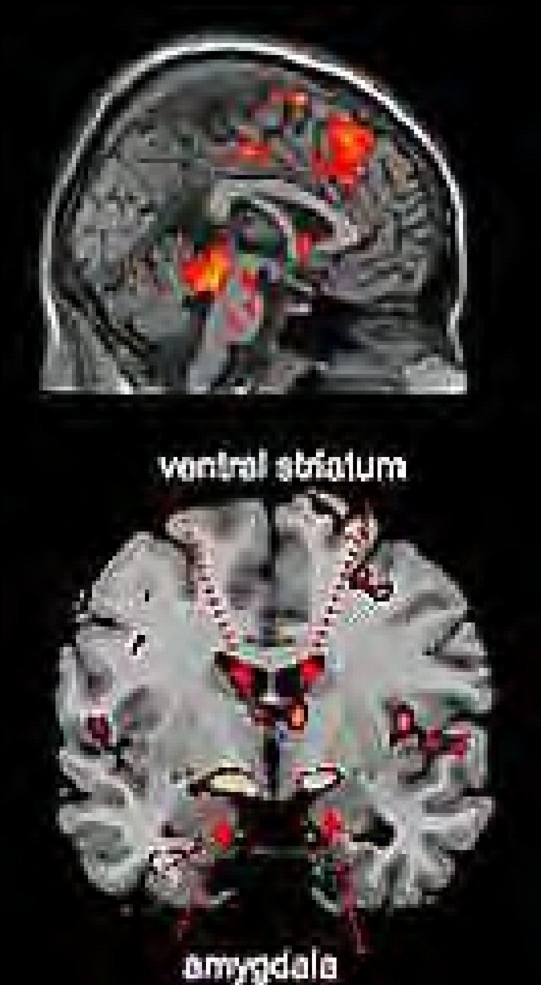
H. Gerry Taylor, PhD,[a] Susan R. Bowen, PhD,[a] Dean W. Beebe, PhD,[b] Elise Hodges, PhD,[c] Raouf Amin, MD,[b] Raanan Arens, MD,[d] Ronald D. Chervin, MD, MS,[e] Susan L. Garetz, MD,[f] Eliot S. Katz, MD,[g] Reneé H. Moore, PhD,[h] Knashawn H. Morales, ScD,[i] Hiren Muzumdar, MD,[j] Shalini Paruthi, MD,[k] Carol L. Rosen, MD,[a] Anjali Sadhwani, PhD,[l] Nina Hattiangadi Thomas, PhD,[m] Janice Ware, PhD,[l] Carole L. Marcus, MBBCh,[n] Susan S. Ellenberg, PhD,[i] Susan Redline, MD, MPH,[o] Bruno Giordani, PhD[c]



Conclusions

As compared with a strategy of watchful waiting, surgical treatment for the obstructive sleep apnea syndrome in school-age children did not significantly improve attention or executive function as measured by neuropsychological testing but did reduce symptoms and improve secondary outcomes of behavior, quality of life, and polysomnographic findings, thus providing evidence of beneficial effects of early adenotonsillectomy.

Children with conduct problems or school discipline referrals, in comparison to peers, have increased symptoms of OSA



Bullies enjoy seeing others in pain:
Brain scans show disruption in natural empathetic response

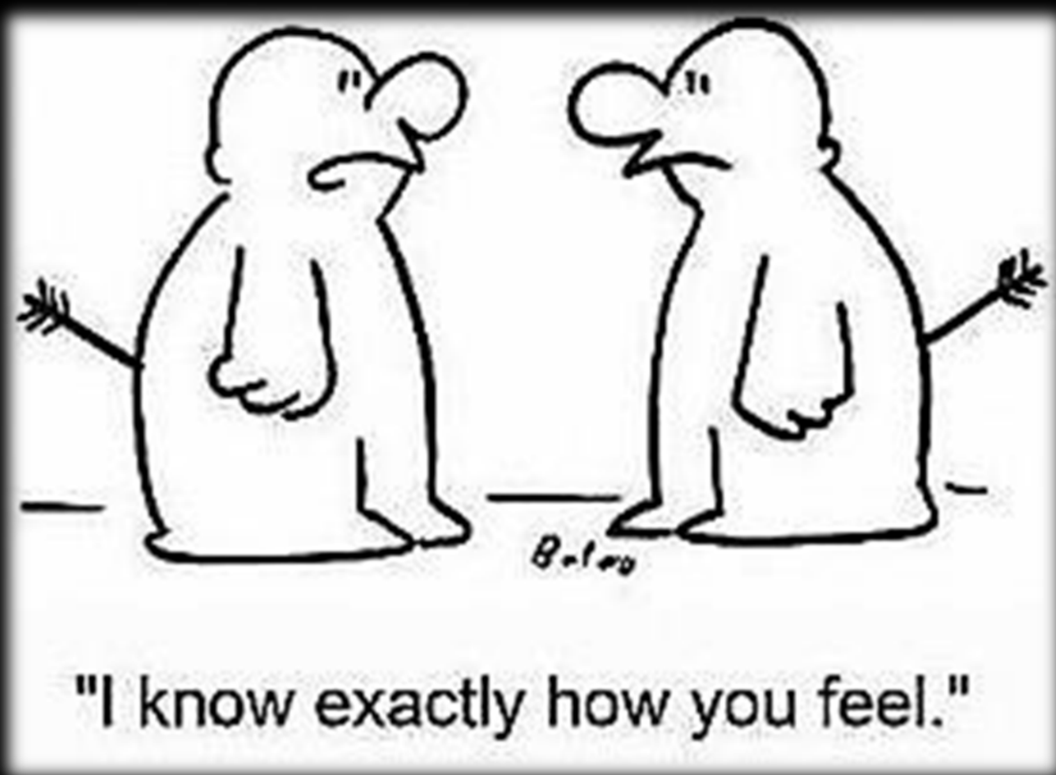
O'Brien et al. Sleep Med, 2011
Decety et al. Biological Psychology, 2008

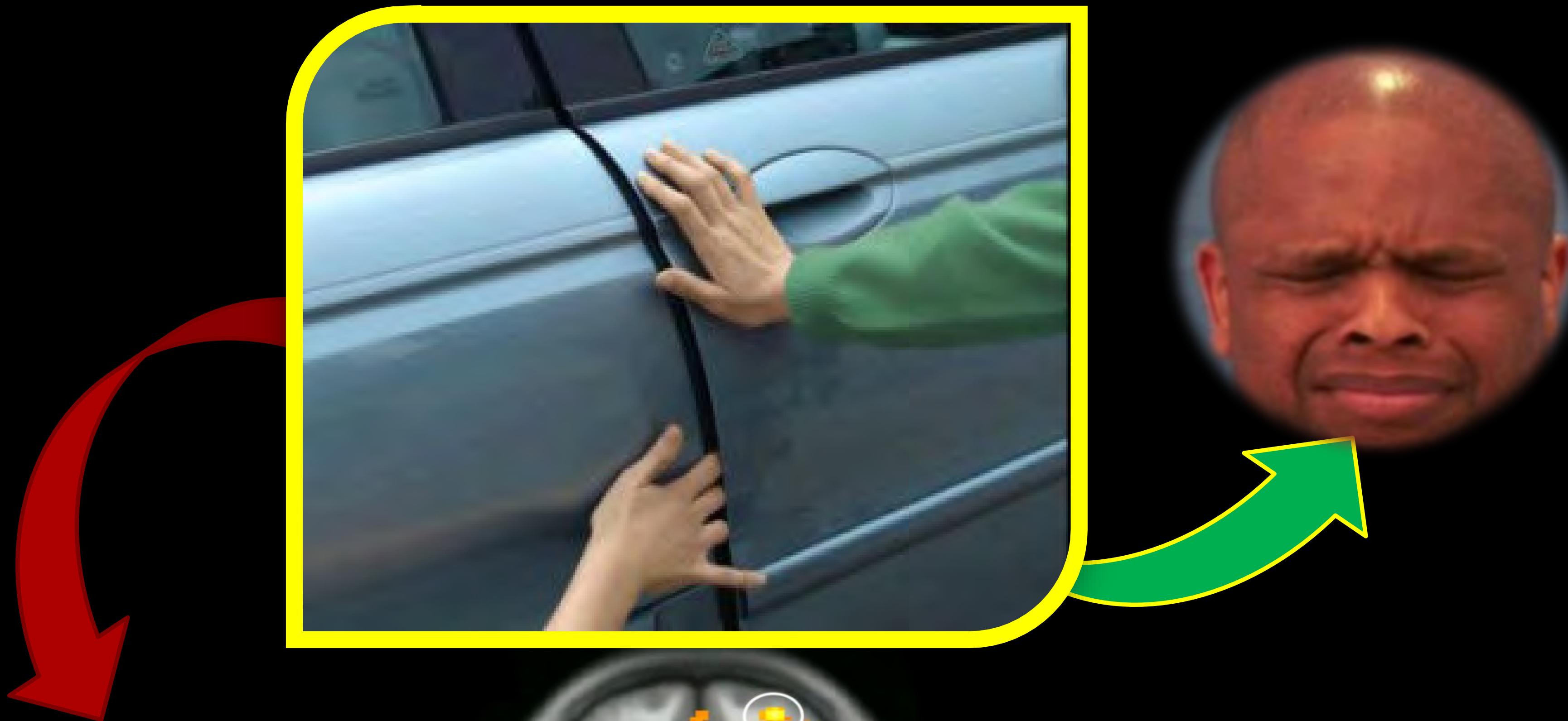
em·pa·thy

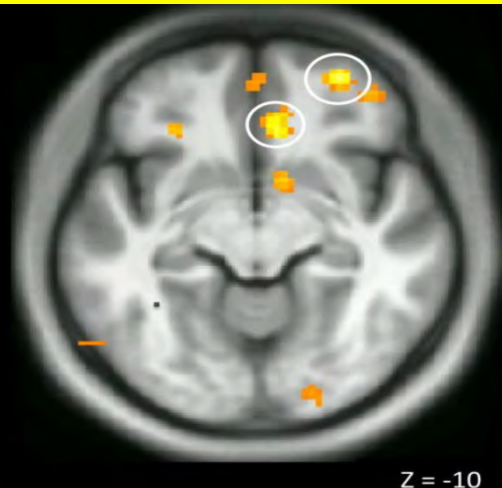
ˈempəTHē/

Noun

The ability to understand and share the feelings of another







Normal individuals show activation of the **amygdala** in response to the perception of intentional harm to others.

Effect of OSA on Empathy-Research Design

Snoring Children
Ages 7-11 Years
PSG in Pediatric Sleep Center

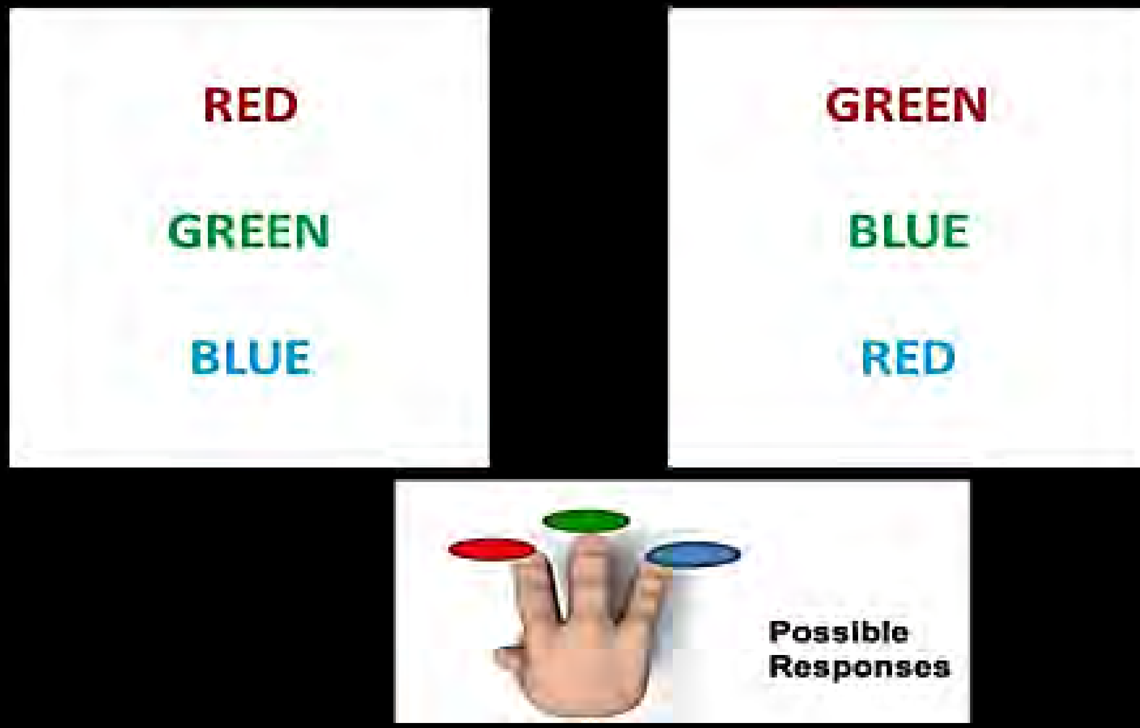
The morning after sleep study:

- **Neurocognitive Battery of Tests (DAS-NEPSY)**
- **Child Behavior Checklist-Revised**

Peabody Picture Vocabulary Test-III

IQ-screening tool
Children select one of four pictures that best correspond to the word the tester read.
Mean of 100 and a standard deviation of 15.

Congruent Incongruent



Stroop Task:

Presenting three color words with letters in red, green, or blue font.
Participants were shown a word and asked to indicate the color of the letters by pressing one of three buttons on a button box.
Congruent and incongruent trials were presented randomly .
While in the scanner, participants were shown 96 color-word combinations.

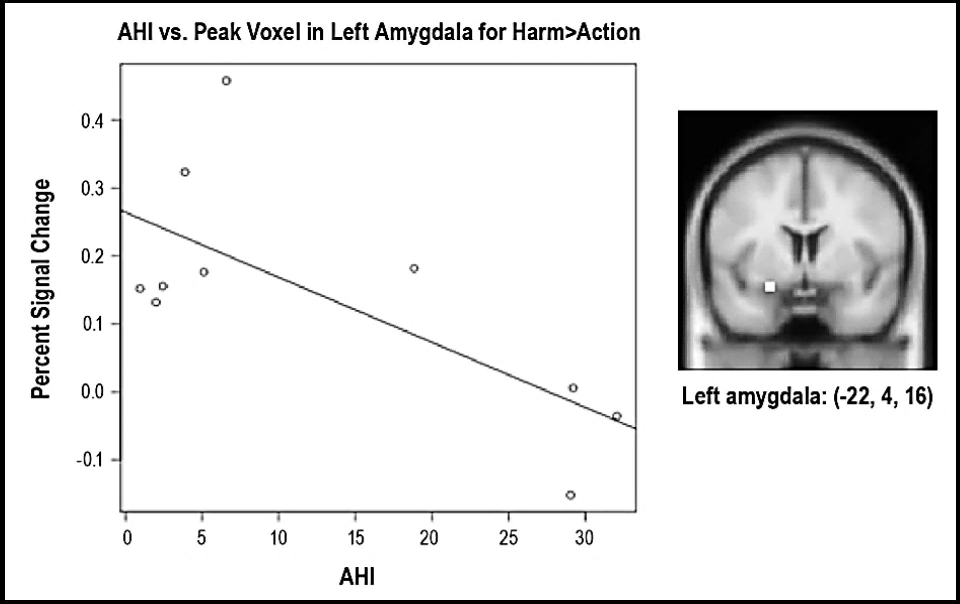
Empathy Task-Test

- Participants viewed 60 dynamic visual scenarios.
- Participants were instructed to lie still and pay attention to the people in the scenes.
- 30 scenes : Neutral actions that did not involve harm

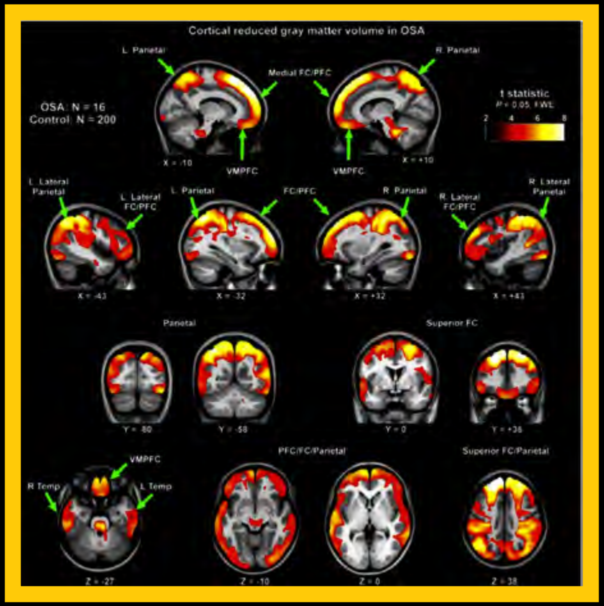
- 30 scenes : Interpersonal harm

Kheirandish-Gozal et al.Sleep 2014

Kheirandish-Gozal et al. Sleep 2014



- Normally developing children have activation of the amygdala in response to the perception of intentional harm to others.
- Children with sleep apnea showed greater recruitment of regions of their brain (implicated in cognitive control, conflict monitoring, and attentional allocation) in order to perform at the same level as children without sleep apnea.
- **AHI** predicted neural responses in left amygdala.
- Increased respiratory disturbance during sleep may lead to **reduced empathy.**



- Normally developing children have activation of the amygdala in response to the perception of intentional harm to others.
- Children with OSA showed **greater regions of their brain** in order to perform at the same level as children without sleep apnea.
- Severity of OSA measured by AHI predicted neural responses in left amygdala.
- Increased respiratory disturbance during sleep may be related to reduced sensitivity in the amygdala.

Brain Volume Reductions?

In multiple MR imaging studies in adult OSA patients, the presence of significant neural and axonal injury has been inferred along with their potential reversibility with treatment

Kumar et al. J Neurosci Res 2012
Fatouleh et al. NeuroImage Clinical 2015
Macey et al.Sleep 2012
Canessa et al. Am J Respir Crit Care Med 2011
Macey et al. Sleep 2008
Cross et al. Sleep 2008
Macey et al. Am J Respir Crit Care Med 2002

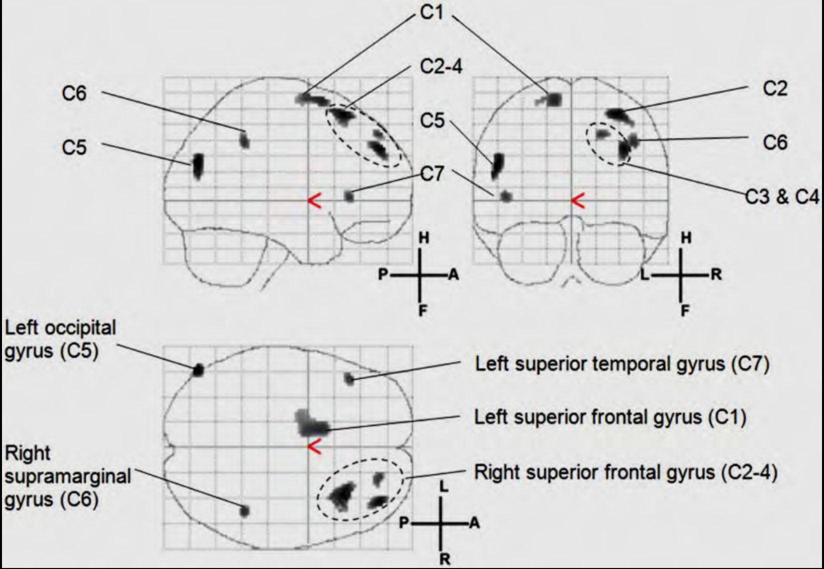
- Children with OSA showed significantly reduced attention and visual-fine motor coordination scores compared with controls. Grey matter volume deficit was observed in prefrontal and temporal regions of cases with moderate-to-severe OSA only.

- Significant negative correlations were found between the visual-fine motor coordination score and the ratio of grey matter volume over total brain volume.

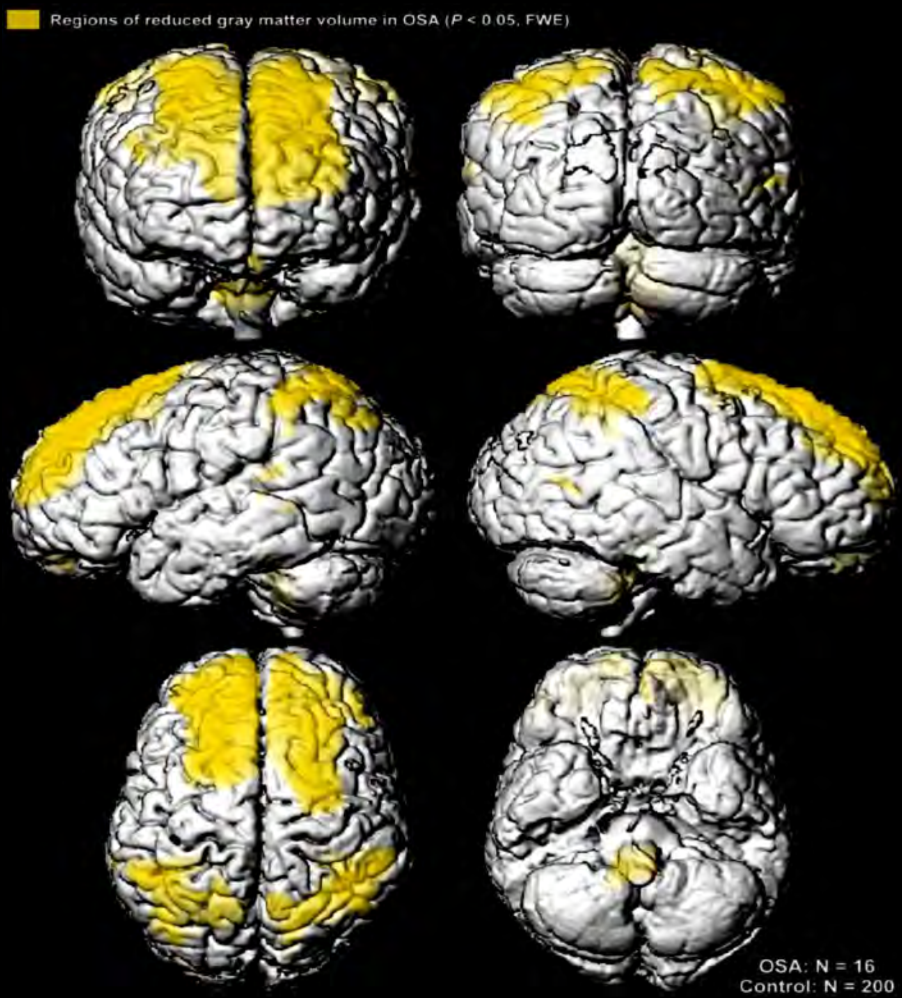
Chan et al. Sleep Medicine ,2014

Maximum intensity projection (MIP) of the statistical map showing areas of grey matter deficits in patients with moderate-to-severe obstructive sleep apnea.

The MIP is projected on a glass brain in three orthogonal planes. Corresponding brain regions: C1, left superior frontal gyrus; C2–4, right superior frontal gyrus; C5, left occipital gyrus; C6, right supramarginal gyrus; C7, left superior temporal gyrus.



In children with OSA, even when cognitive deficits are not detectable by psychometric tests, there are detectable gray matter losses.



Philby et al. Scientific Reports, 2017

SCIENTIFIC REPORTS

OPEN

Reduced Regional Grey Matter Volumes in Pediatric Obstructive Sleep Apnea

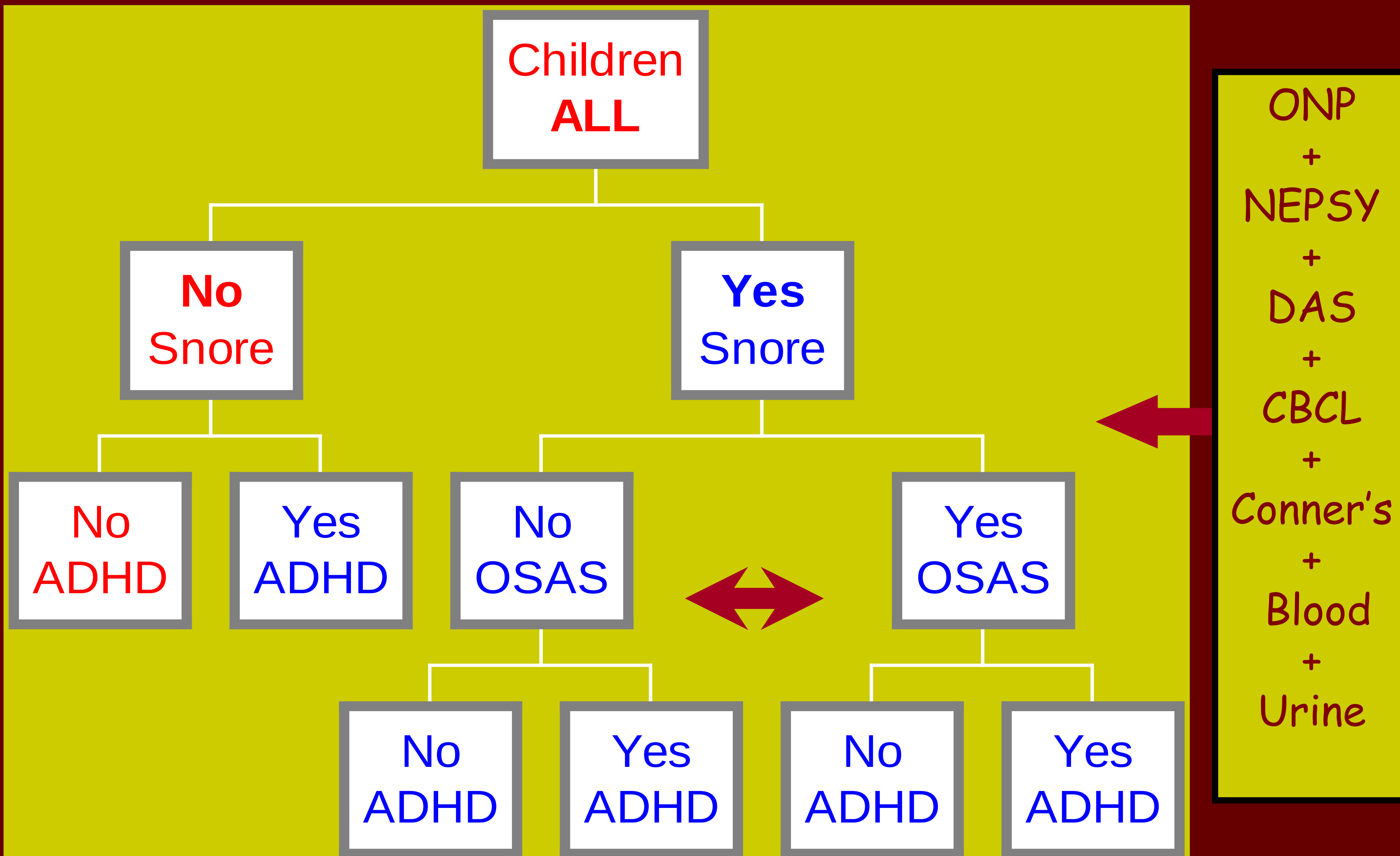
Received: 02 December 2016
Accepted: 07 February 2017

Mona F. Philby[1], Paul M. Macey[2,3], Richard A. Ma[2], Rajesh Kumar[3,4,5,6], David Gozal[1] & Leila Kheirandish-Gozal[1]

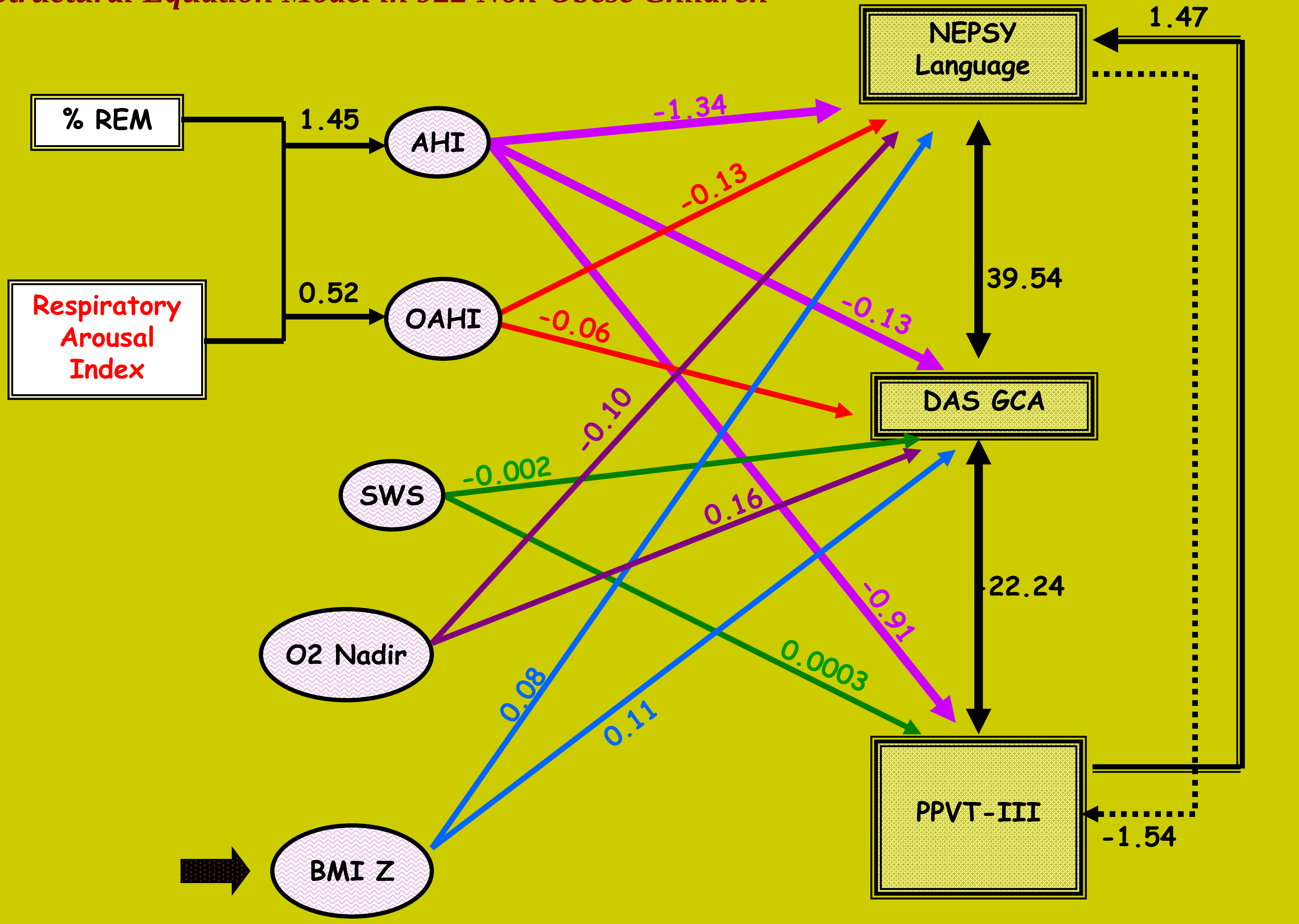
- In a cohort of 7–11 year-old children clinically and PSG diagnosed with OSA, extensive regionally-demarcated grey matter volume reductions are present.
- These regional brain changes were **not correlated** with the severity of respiratory disturbance during sleep and there were **no trends** indicative of an association with cognitive ability.
- Since determining OSA duration is not practically possible, subjects may have experienced OSA for several years, and these findings may either reflect delayed neuronal development or disease induced neuronal damage.
- The nature of the grey matter volume changes is unclear. (atrophy arising from neuronal damage?)


>120
90 -120
< 90
OSA
90 -120
< 90
75-90

Louisville Study



Structural Equation Model in 922 Non-Obese Children



Some Good News!

- Prospective detection of low SES young children (3-4 years) who habitually snored uncovered not only that they were more likely to have cognitive deficits but also that if treated for OSA, the cognitive deficits would completely reverse.
  (Montgomery Downs et al, 2005)

- Similar findings by Friedman et al (Sleep, 2003) in a general pediatric population

Early Detection and Intervention

- What is the impact of T&A in preschool-age children with OSA in a highly vulnerable, at-risk community population diagnosed prospectively through screening?

Methods

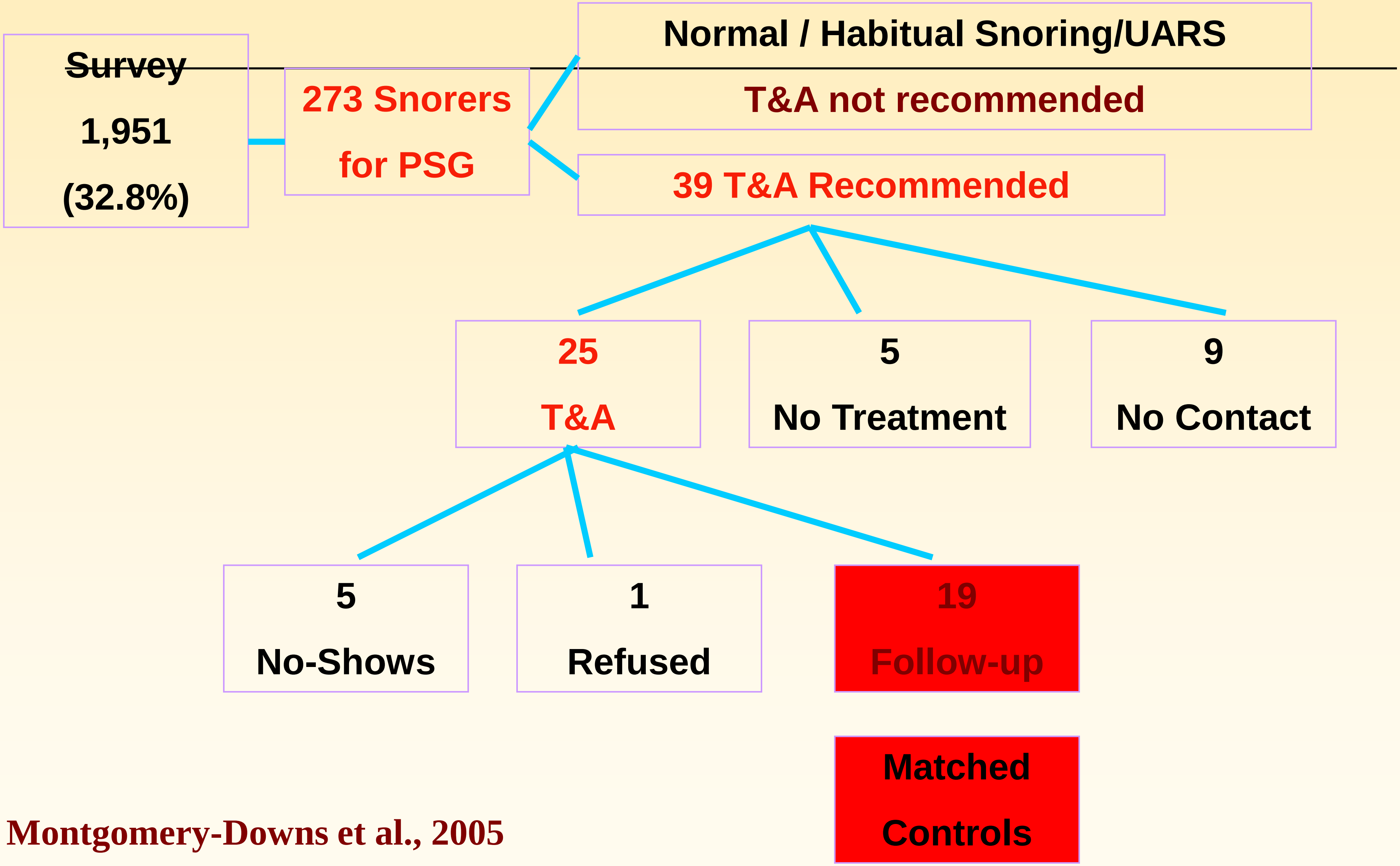
- Validated questionnaire to parents of Jump Start students
  - Presence of snoring
  - ≥3 days/week
  - ≥ Medium-Loud

- PSG
  - Diagnostic
  - ≥3 months Post-operative

- Cognitive Assessment

Montgomery-Downs et al., 2005

Methods



Montgomery-Downs et al., 2005

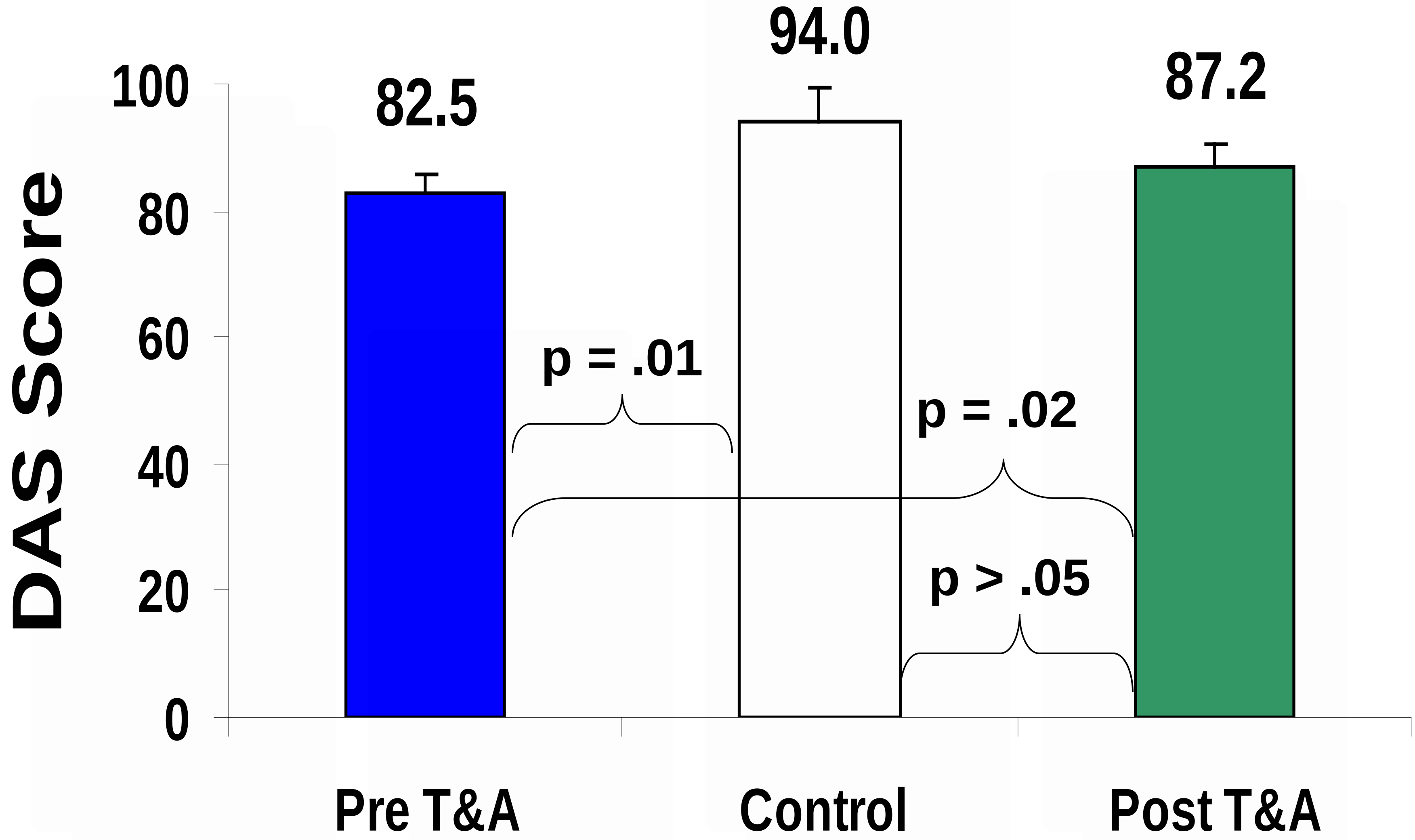
Differential

Ability

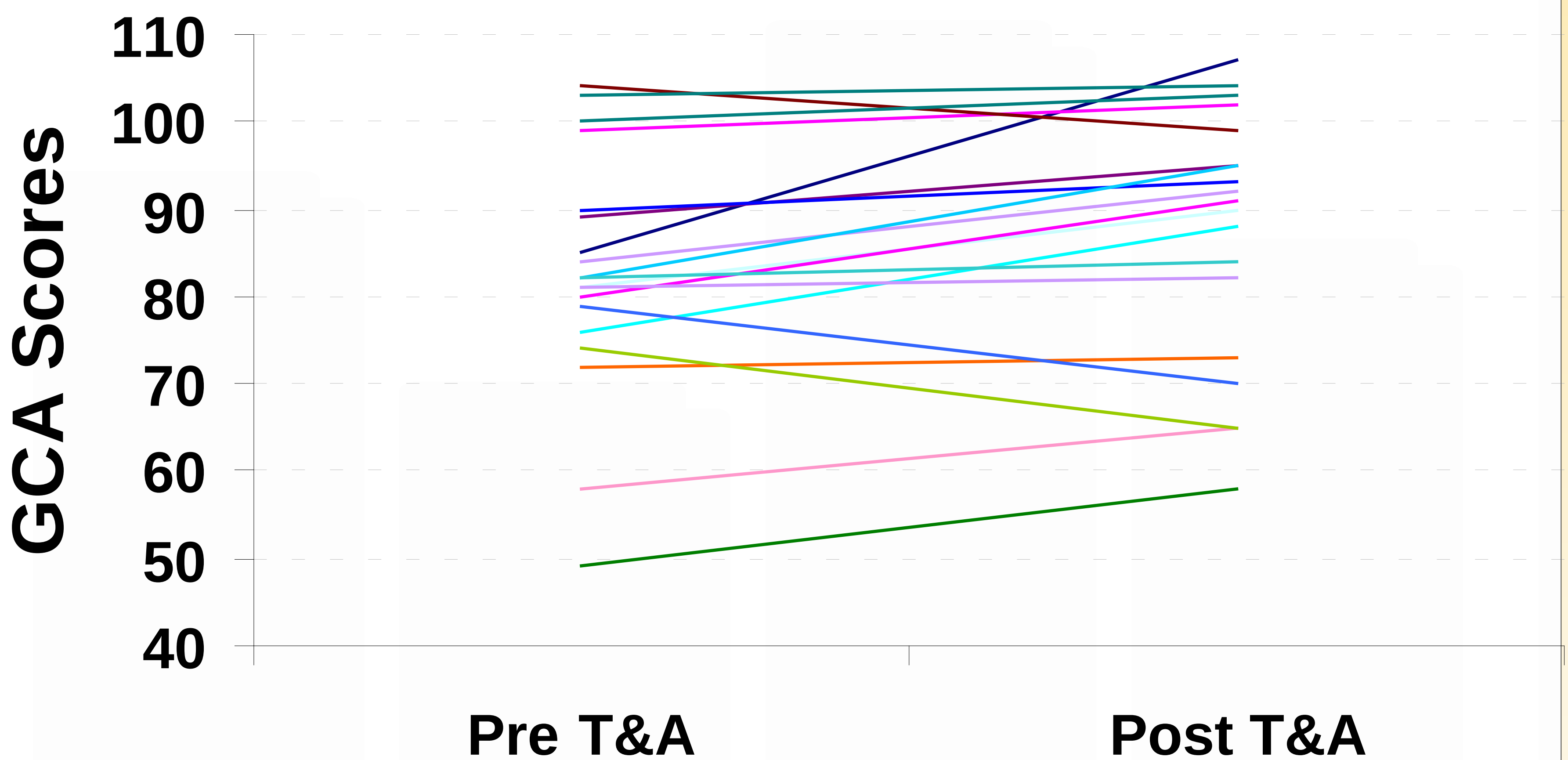
Scales

Mean = 100

SD = 15



DAS Score
100
80
60
40
20
0
82.5
94.0
87.2
p = .01
p = .02
p > .05
Pre T&A
Control
Post T&A



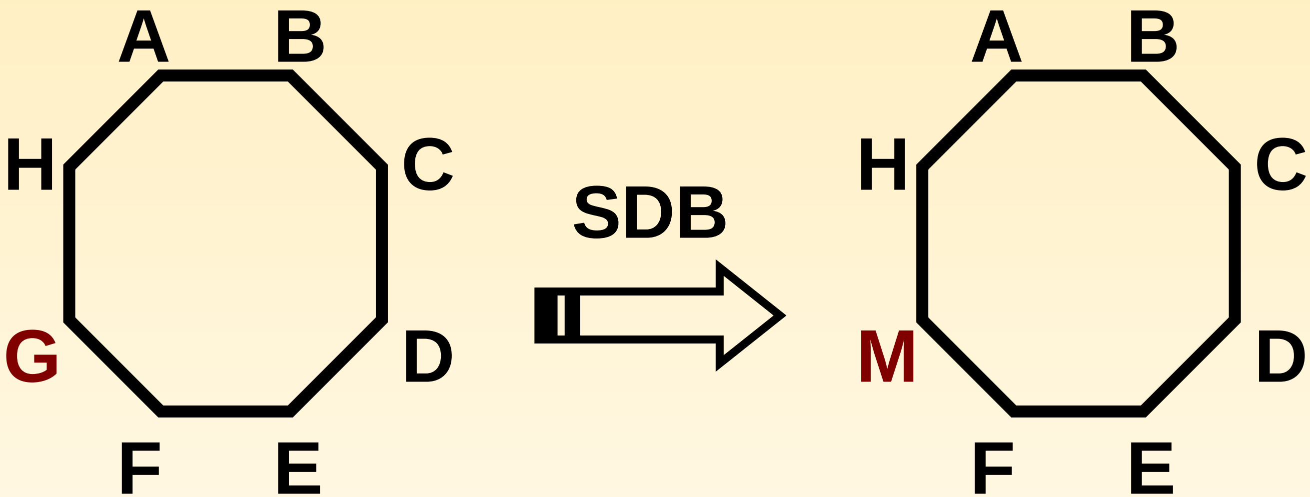
Montgomery-Downs et al., 2005

Summary

- Sleep-disordered breathing in children displays dose-dependent adverse effects on several neurobehavioral measures.
- Attention deficits seem to be more dependent on sleep fragmentation, while both behavior and mental processing (pre-frontal cortex executive function) are more affected by respiratory disturbance and oxygenation.

2nd Best Theory

2000 MHz chip **800 MHz chip**



Simple Computation: 0.32 ms vs 0.44 ms

Complex Computation: 2.23 ms vs “FREEZE”

Summary

Sleep disordered breathing in children displays dose-dependent adverse effects on several neurobehavioral measures.

Problem I

Children with:

- *OSA:* *AHI> 2, SaO2 nadir <92%; respiratory arousal index >2*
- *PS:* *snoring, AHI <1, SaO2nadir>92%, respiratory arousal index <2*
- *CO* *No snoring, normal sleep study as in PS*

Matched for :

- *Age*
- *Gender*
- *Ethnicity*
- *BMI z score*
- *maternal education*

Test for behavioral and cognitive function

Behavioral Measures

	PS (n=150)	OSA (n=150)	Control (n=150)
CBCL (Child behavior Check List)			
Withdrawn	56.0 ± 8.1	55.1 ± 6.8	54.3 ± 6.8
Somatic Complaints	59.0 ± 8.2*	61.2 ± 9.5*	55.7 ± 6.3
Anxious / Depressed	57.5 ± 8.0	57.2 ± 9.8	55.2 ± 6.2
Social Problems	57.8 ± 8.8*	58.9 ± 9.5	54.4 ± 6.7
Thought	57.9 ± 8.3	56.9 ± 8.4	55.8 ± 6.4
Attention	61.1 ± 10.6*	59.7 ± 9.4	57.3 ± 7.7
Delinquency	57.5 ± 7.9*	59.2 ± 8.6*	54.2 ± 5.8
Aggression	58.5 ± 10.3*	59.2 ± 9.6	55.5 ± 6.1
Internalizing	56.3 ± 10.9*	56.4 ± 11.6*	51.0 ± 11.3
Externalizing	55.7 ± 11.9	56.7 ± 13.0	52.3 ± 9.5
Total	59.0 ± 11.6*	59.1 ± 11.7	53.7 ± 11.1

Gozal D, et al unpublished

Neurocognitive Measures

	PS (n=150)	OSA (n=150)	Control (n=150)
DAS (Differential Ability Scales)			
Verbal	96.5 ± 13.0**	92.9 ± 11.3**	105.4 ± 13.2
Non-Verbal	99.1 ± 13.0	96.1 ± 12.6*	103.3 ± 13.7
Overall	97.9 ± 12.9**	94.2 ± 10.6**	105.2 ± 12.4
NEPSY			
Attention / Executive function	105.2 ± 16.1*	103.7 ± 16.4	110.9 ± 14.8
Language and communication	98.2 ± 17.3*	95.7 ± 16.2*	105.6 ± 17.6
VisuospatialFunctions	102.6 ± 15.2*	100.2 ± 14.2*	108.6 ± 13.3
Learning and Memory	108.2 ± 16.0	108.6 ± 16.7	110.8 ± 13.9

Gozal D, et al unpublished

Effect of OSA on Behavior Large Community Cohort

- n=1022
- All races and socioeconomic backgrounds
- Snoring and non-snoring
- Ages 5–7 years
- Prospective recruitment from community
- Polysomnography
- Behavioral assessments

Divided into 4 groups:

- Group 1: Non-snoring and AHI <1
- Group 2: Snoring and AHI <1
- Group 3: Snoring and AHI 1–5
- Group 4: Snoring and AHI >5

Smith et al. Pediatric Pulmonology & Sleep. 2016

The Child Behavior Checklist – Revised (CBCL)

Parent report scale for (5-17 years) measuring problem behaviors and mood challenges in children. yields T-scores with a mean±SD of 50±10

Subscales:

1. Withdrawn
2. Somatic Complaints
3. Anxious/Depressed
4. Social Problems

Internalizing problems

5. Thought Problems
6. Attention-Hyperactivity Problems
7. Delinquent Behavior
8. Aggressive Behavior

Externalizing problems

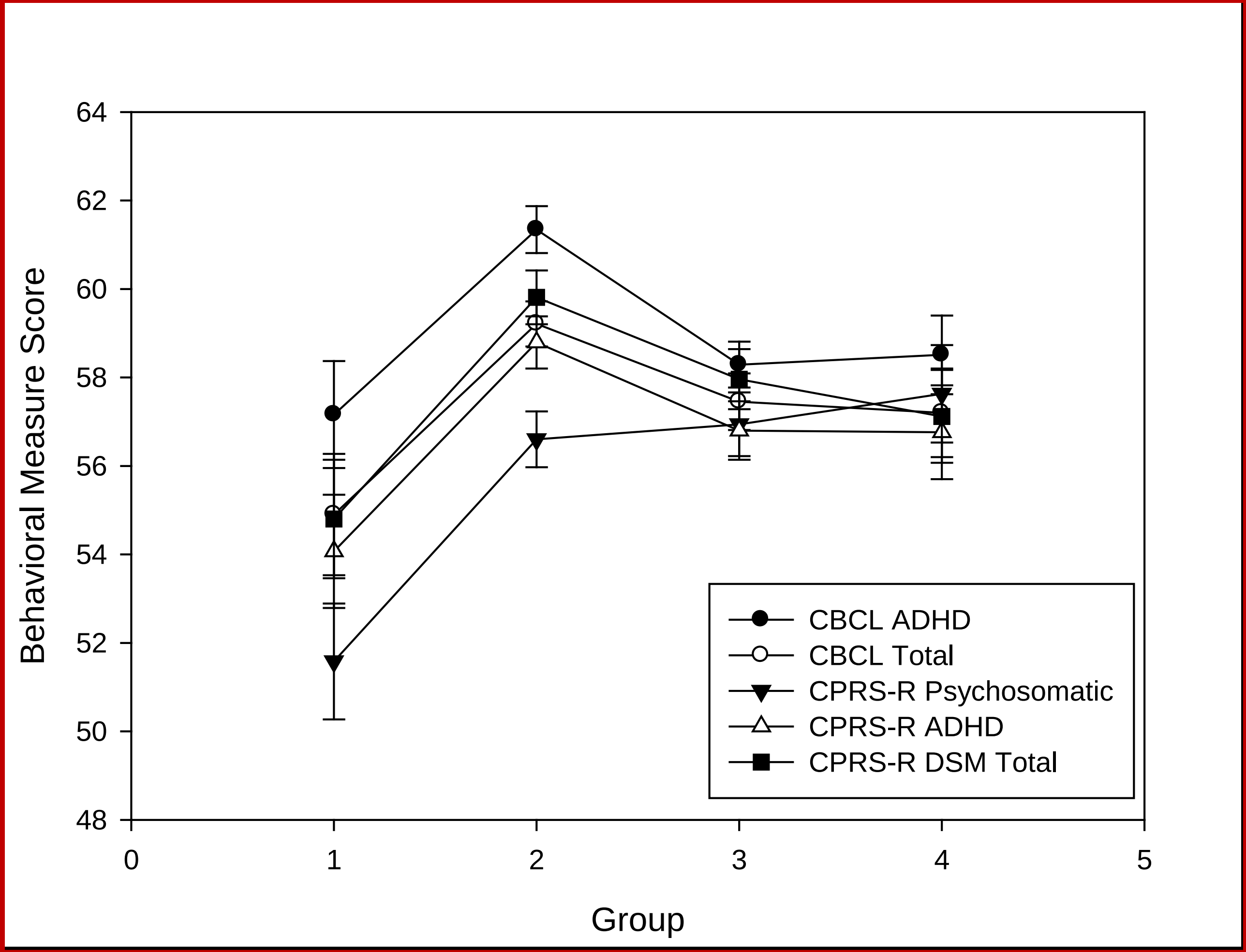
The Conners' Parent Rating Scales – Revised (CPRS-R)

Parent report scale, for 93-17 years) examining the presence and severity of problem behaviors observed in children.

Subscales:

1. Oppositional
2. Cognitive Problems
3. Inattention
4. Hyperactivity
5. Anxious-Shy
6. Perfectionism
7. Social Problems
8. Psychosomatic ratings

Behavior is at its worst in "Primary Snoring Group"



All 10 behavioral variables differed significantly between Group 1 (no snore, AHI<1) and all other groups.

Post hoc comparisons indicated that snore only Group was the most impaired for most behavioral measures.

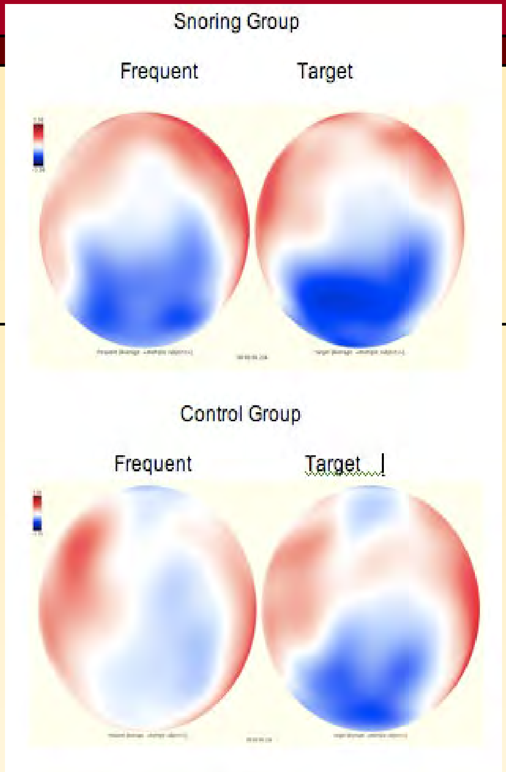
This study suggests that OSA during early childhood is a significant contributor to challenges with attention and behavioral regulation, as rated by parents.

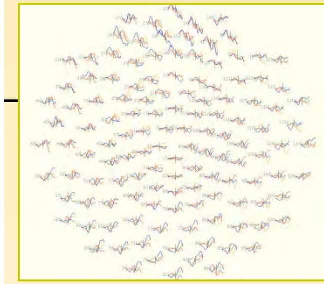
ORIGINAL ARTICLE
PAEDIATRIC PULMONOLOGY AND SLEEP

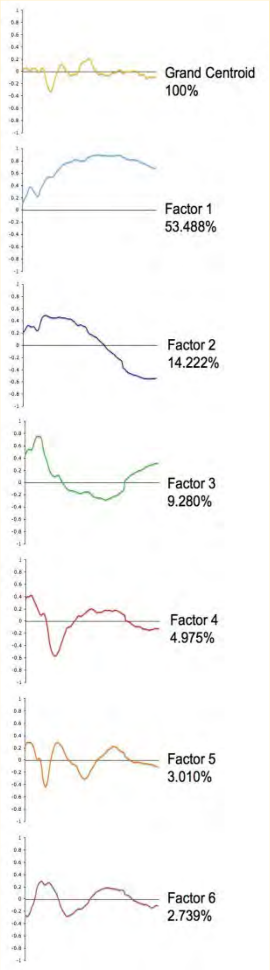
CrossMark

Impact of sleep disordered breathing on behaviour among elementary school-aged children: a cross-sectional analysis of a large community-based sample

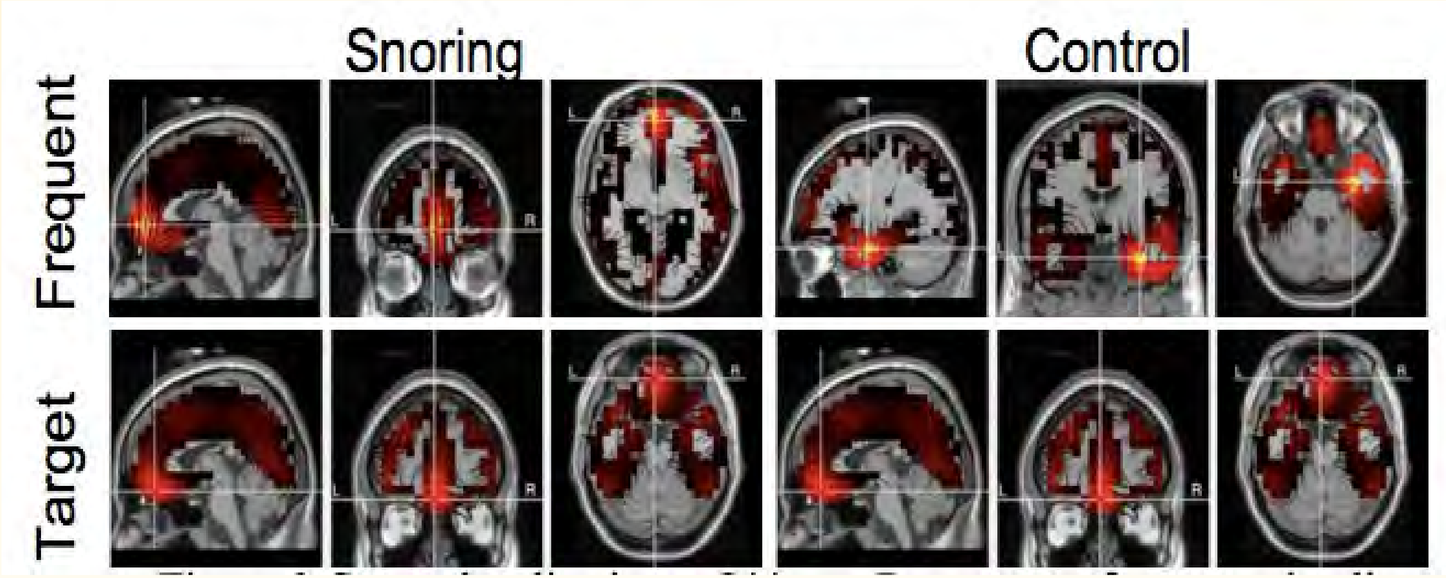
Dale L. Smith[1,2], David Gozal[3], Scott J. Hunter[3,4], Mona F. Philby[3], Jaeson Kaylegian[4] and Leila Kheirandish-Gozal[3]







Barnes et al, 2009

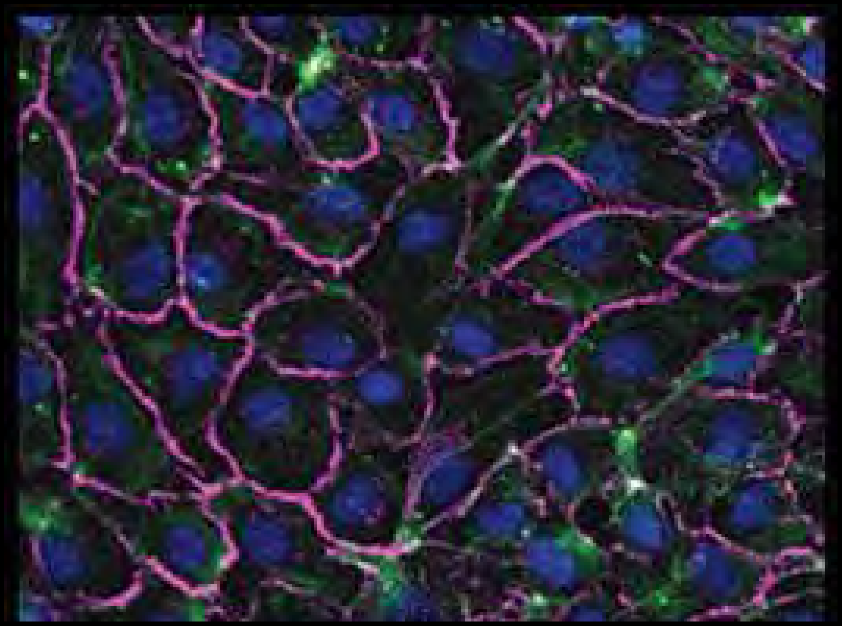


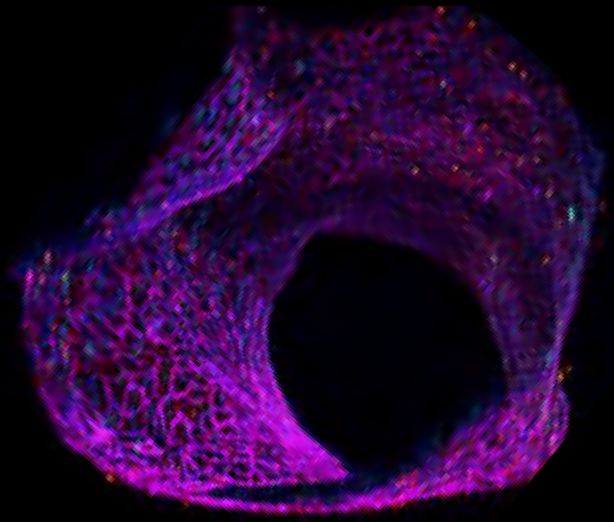
en·do·the·li·um

ˌendəˈTHēlēəm/

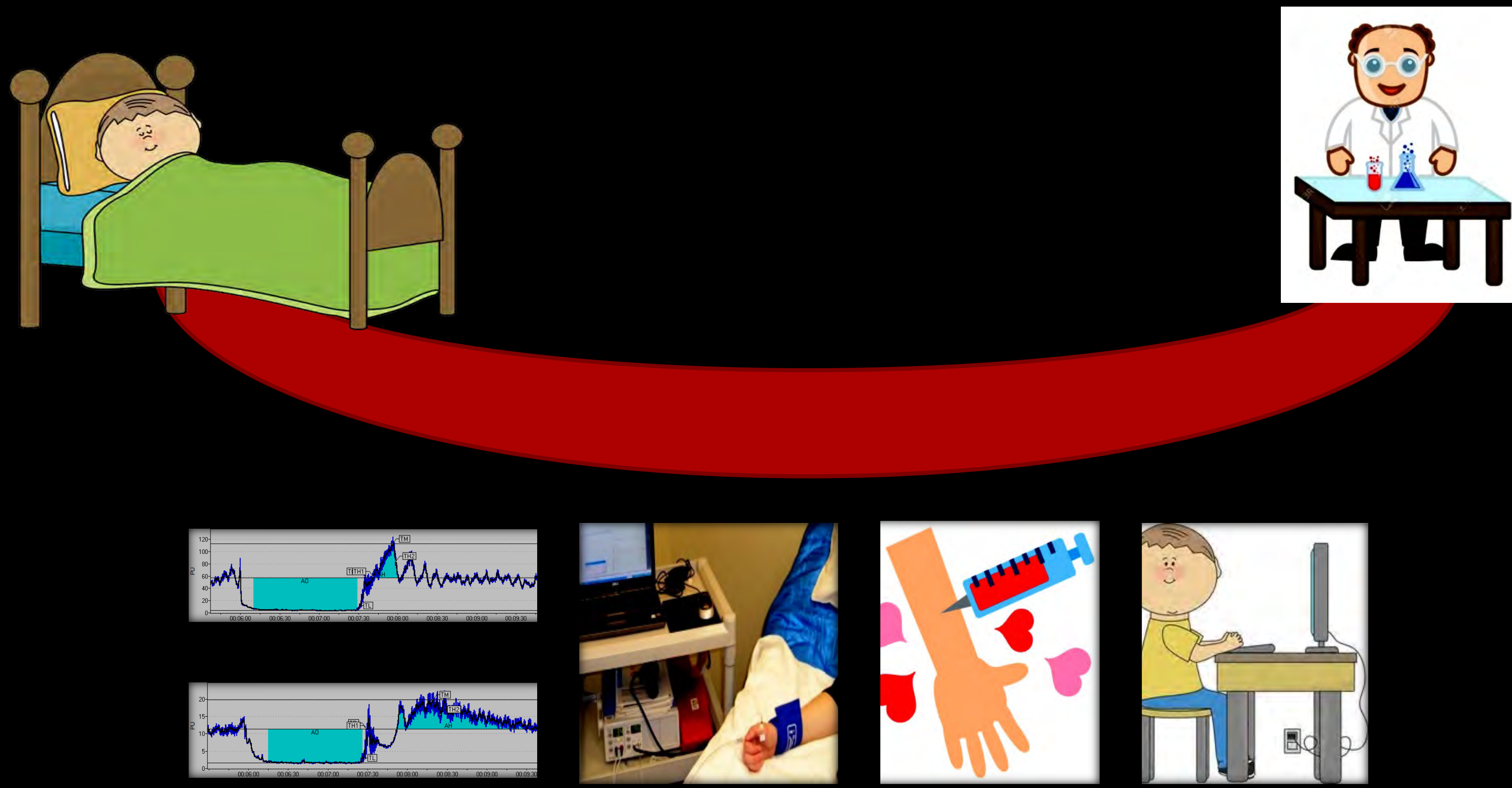
noun

Single layer of cells lining the blood vessels

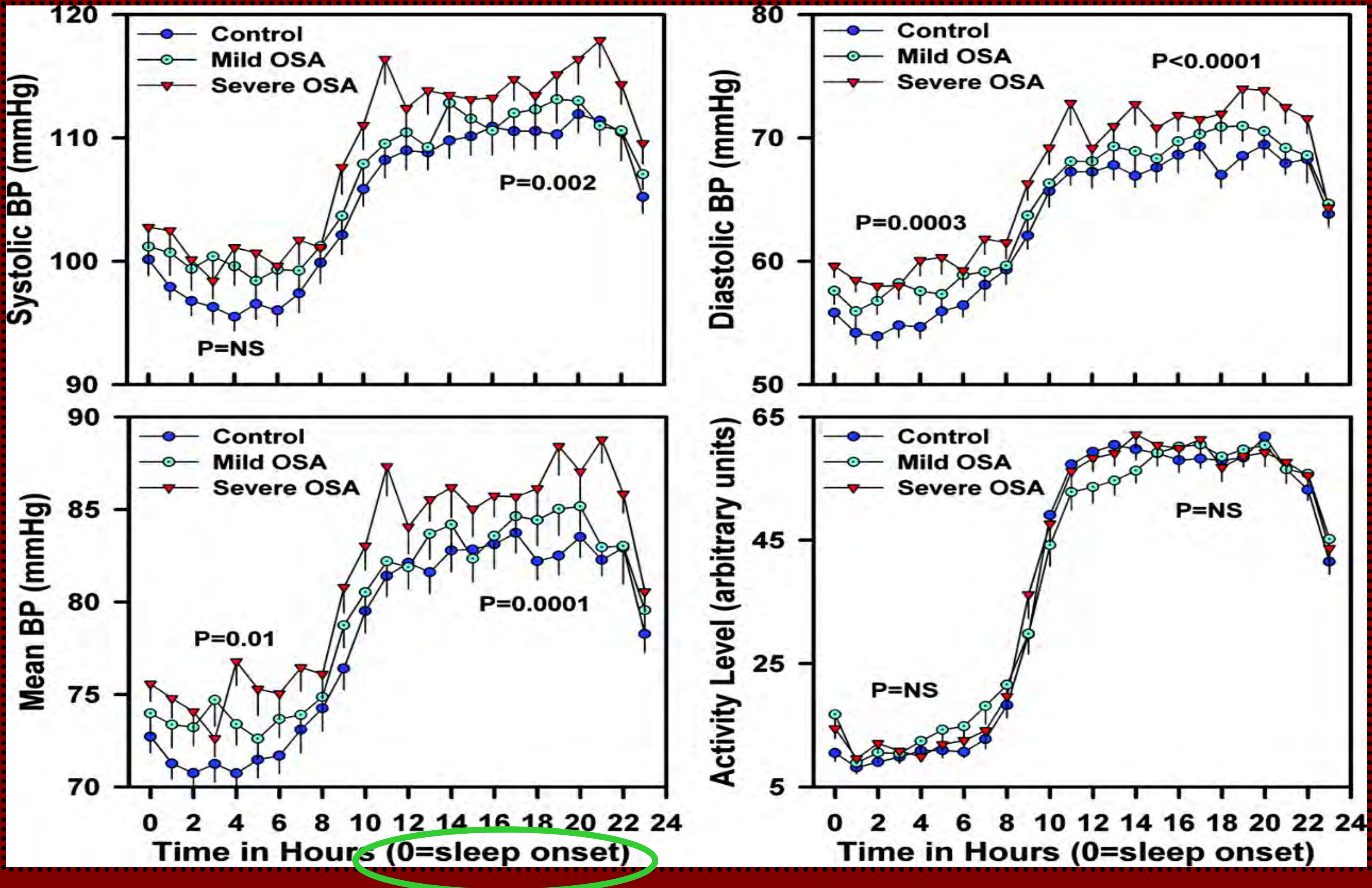




fluorescence confocal microscopy of the blood-brain barrier.
Credit: Wyss Institute at Harvard University

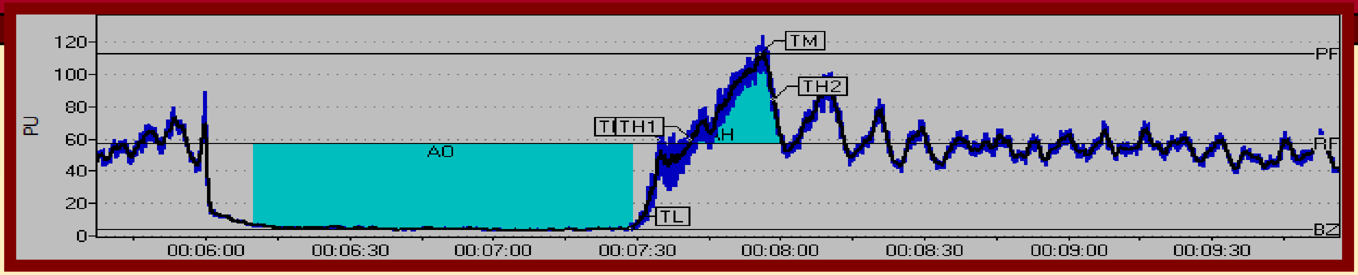


24-hour ambulatory BP synchronized at sleep onset

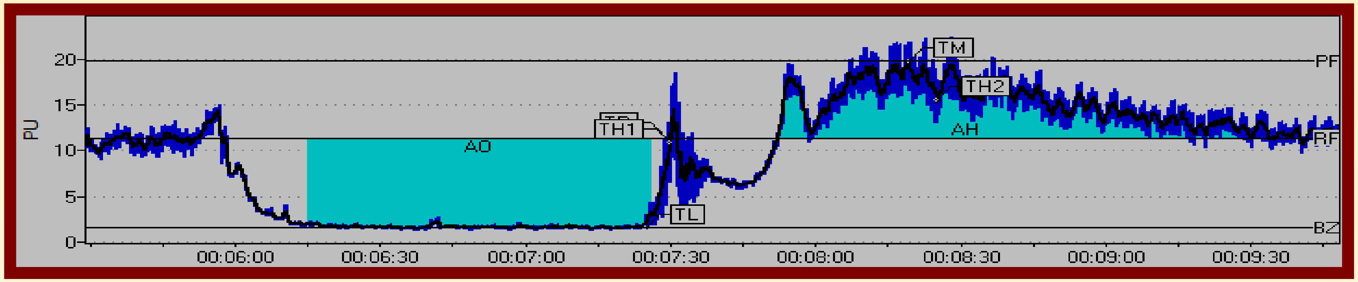


*The absence of **sleep onset BP dipping***
The more severe the OSA the more increases in BP occurred.

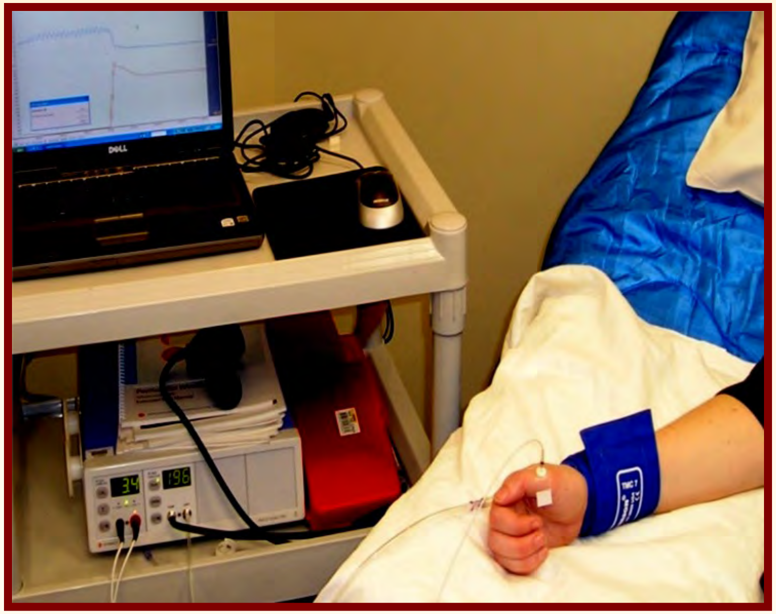
Amin et al. Hypertension 2008



Control

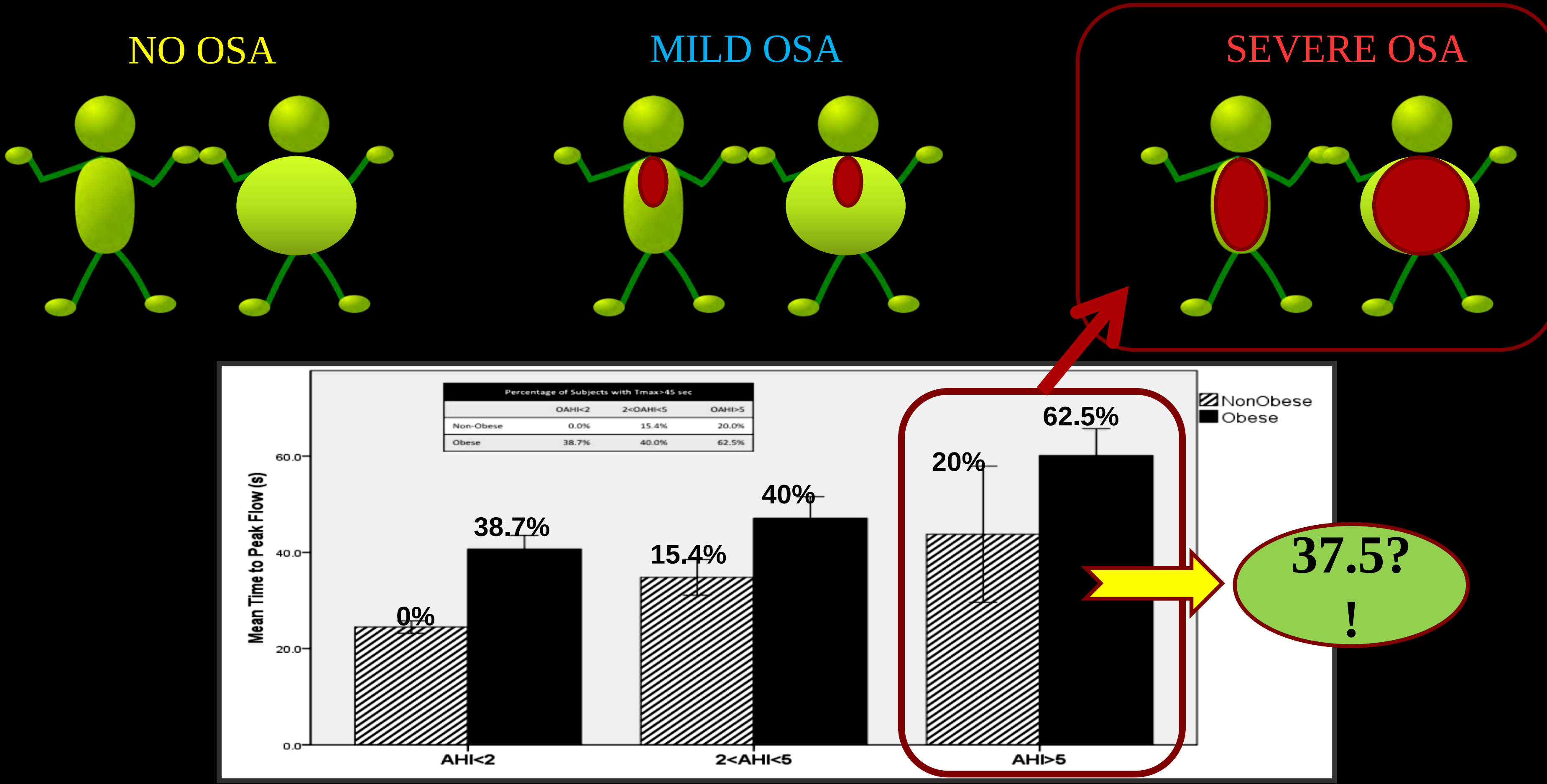


OSA



	OSA n (n=7)	OSA ab (n=7)
Age (years)	7.0±1.0	7.1±1.1
Gender (male, %)	57	57
AHI (events/ hour)	16.7±5.5	17.3±8.4
Peak hyperemic response (sec)	33.2±4.1*	47.8±2.0*

Kheirandish-Gozal et al. CHEST 2013



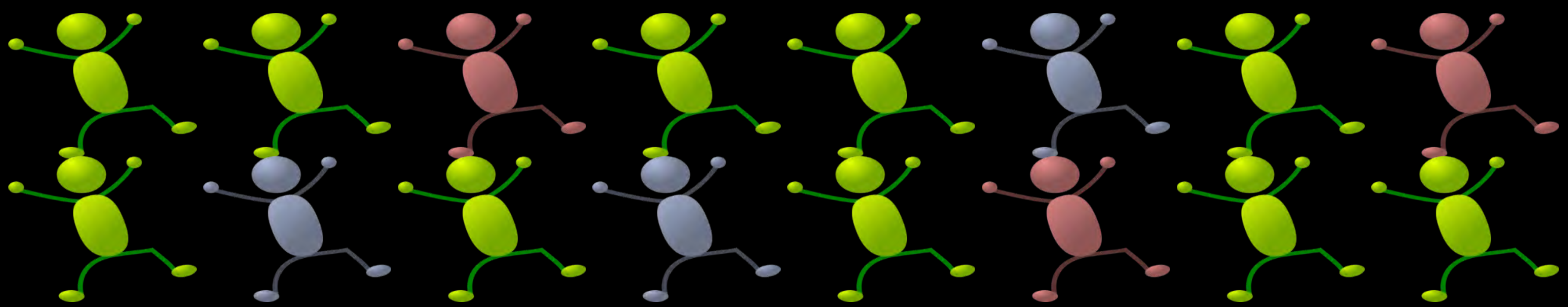
Bhattacharjee et al. CHEST 2012

WHY

At any given AHI,

only some children present with

endothelial dysfunction ?

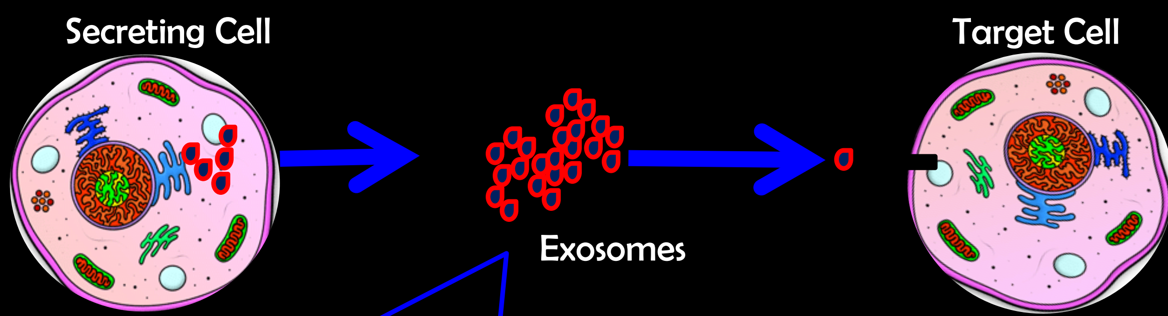


exosome

ex·o·some

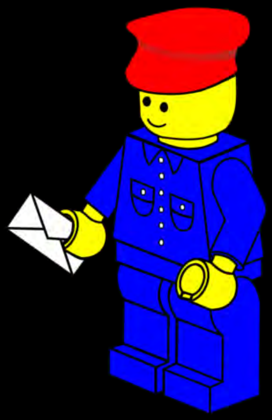
noun

A tiny vesicle created and released from the plasma membrane of various types of cells, especially immune cells, and capable of inducing antigen-specific immune responses



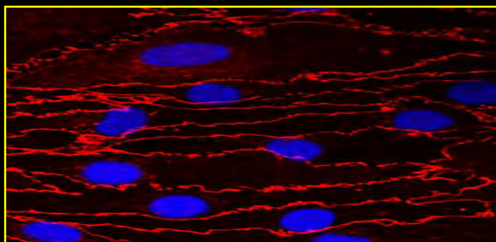
Specialized membranous nano-sized vesicles
Vehicle for cell-free intercellular communication.
Secreted by many cell types including B cells, T cells , dendritic cells , mast cells, platelets , and tumor cells .
In response to physiological and/or pathological signals.
Secreted in biological fluids (blood/urine/plasma/breast milk/saliva).
Contain functional mRNA , miRNA (function as post-transcriptional regulators of gene expression) , proteins, and lipids.
May be exploited as biomarkers in the diagnosis of disease.

<u>Exosomes</u> are the
FedEx /DHL courier in our bodies

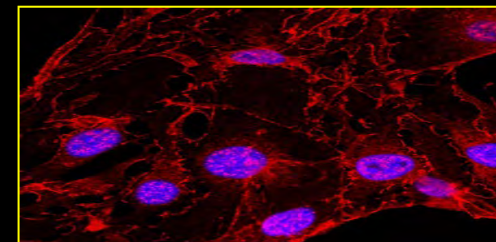


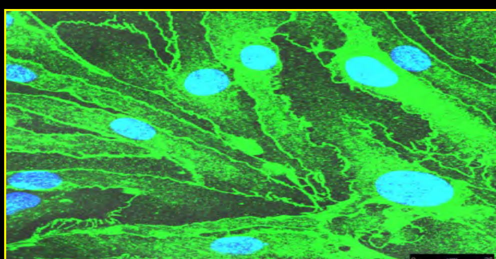
OSA + Normal Endothelial Function

OSA + Endothelial Dysfunction

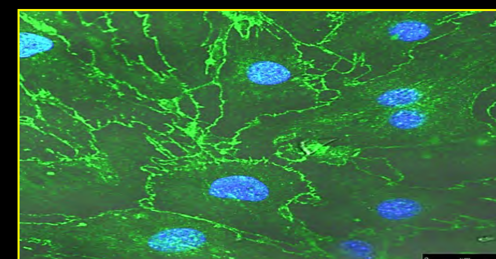


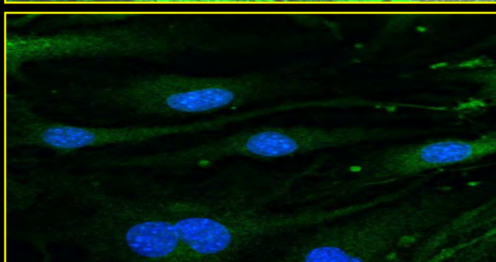
VE-Cadherin
Vascular endothelial adhesion
CD 144



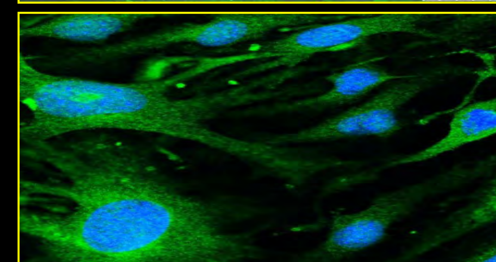


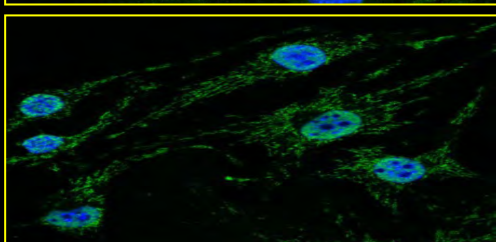
ZO-1
Tight junction protein



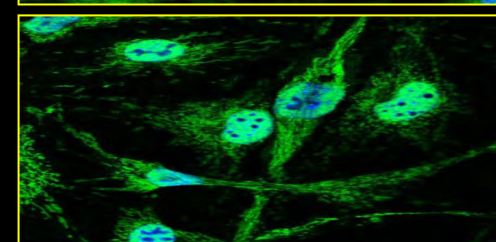


ICAM-1
Intra cellular Adhesion molecule 1
CD54

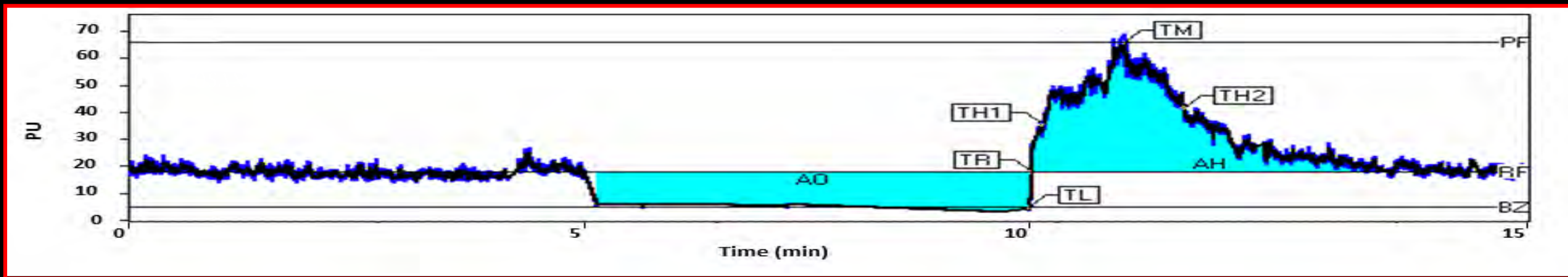




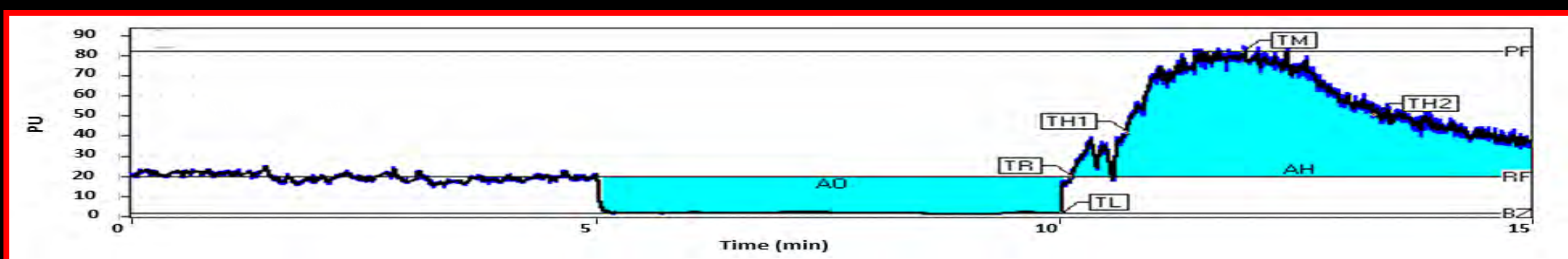
VCAM1
Vascular cell adhesion molecule 1
CD106



Exosome-mediated in vivo effects on vascular function in mice



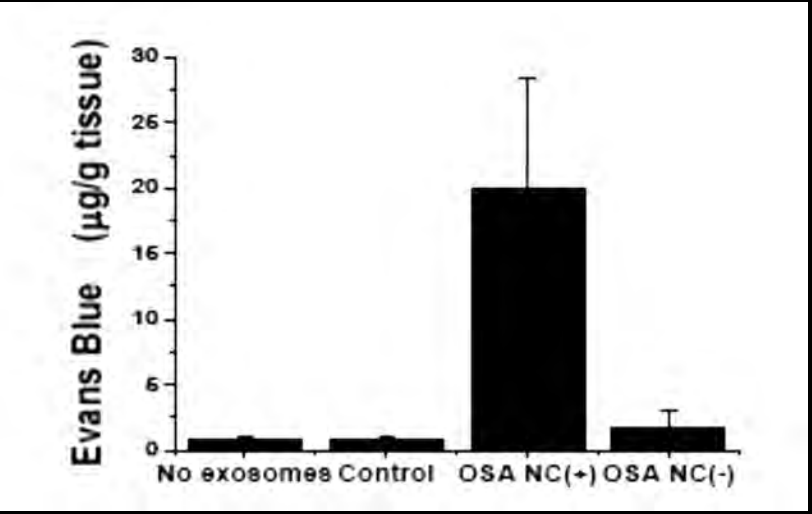
Post occlusive reperfusion kinetics
5 min occlusion time
mouse injected once daily for 3 days



In vivo Evans Blue BBB permeability assessments in mice injected IV with :

- PBS /No exosomes
- Exosomes from healthy control children (CONTROL)
- Exosomes from children with OSA and neurocognitive deficit (OSA NC +)
- Exosome from children with OSA but no cognitive deficits (OSA NC -)

There is significant increased in blood brain barrier permeability induced by exosomes from exosomes of children with OSA associated with cognitive deficits



(n=15/group)

Khalyfa et al, 2022,2023

PS and Cardiovascular Morbidity

Children with OSA were found to have higher daytime and nocturnal diastolic blood pressure than subjects with PS, and those with PS greater daytime systolic and diastolic BP compared to healthy controls without snoring.

Marcus CL et al. Am J Respir Crit Care Med 1998
Kwok KL et al. Chest 2003

No difference in systolic and diastolic pressure during sleep between children with OSA and PS were detected.

Amin R, et al. Am J Respir Crit Care Med 2004

Children with PS have been shown to have elevated systemic blood pressures as well as abnormalities in arterial wall rigidity.

Kaditis AG et al. Pediatr Pulmonol 2005
Amin R, et al. Hypertension 2008
Li AM et al.J Pediatr 2009

Of note PS may also increase BP

Table III. Daytime and nighttime BP measurements in patients with SDB

	Controls (n = 56)	PS (n = 46)	AHI 1 to 3 (n = 62)	AHI > 3 (n = 26)	*P* (trend)
Daytime BP measurements					
SBP, mmHg	107.5 ± 6.8	110.4 ± 7.4	109.9 ± 7.8	110.8 ± 5.3	.042
DBP, mmHg	69.6 ± 3.9	71.7 ± 5.2	71.2 ± 4.3	72.6 ± 4.5*	.008
MAP, mmHg	82.3 ± 4.1	84.2 ± 5.4	83.8 ± 4.7	85.3 ± 4.1*	.014
SBP z-score	-0.67 ± 0.85	-0.23 ± 1.02	-0.33 ± 1.04	-0.23 ± 0.76	.042
DBP *z*-score	-0.41 ± 0.63	-0.06 ± 0.87	-0.15 ± 0.72	0.09 ± 0.75*	.008
MAP *z*-score	-0.31 ± 0.58	-0.01 ± 0.84	-0.10 ± 0.71	0.11 ± 0.64	.019
Systolic hypertension, n (%)	0 (0)	2 (4.3)	4 (6.5)	0 (0)	.39
Diastolic hypertension, n (%)	0 (0)	2 (4.3)	1 (1.6)	1 (3.8)	.39
Nighttime BP measurements					
SBP, mmHg	95.4 ± 6.9	97.6 ± 7.9	98.2 ± 7.8	101.8 ± 8.8†	.0009
DBP, mmHg	56.5 ± 4.9	59.6 ± 5.9*	59.0 ± 4.5*	61.7 ± 6.4‡	.0001
MAP, mmHg	70.9 ± 4.7	73.2 ± 5.8	73.2 ± 4.7	76.3 ± 6.0‡	.0001
SBP z-score	-0.26 ± 0.85	0.06 ± 0.96	0.14 ± 0.99	0.54 ± 1.08†	.0005
DBP *z*-score	0.19 ± 0.82	0.75 ± 0.99†	0.65 ± 0.77*	1.05 ± 1.09‡	.0001
MAP z-score	0.28 ± 0.71	0.64 ± 0.82	0.64 ± 0.69*	1.03 ± 0.86‡	< .0001
Systolic hypertension, n (%)	1 (1.8)	1 (2.2)	4 (6.5)	4 (15.4)	.013
Diastolic hypertension, n (%)	1 (1.8)	9 (19.6)§	5 (8.1)	8 (30.8)§	.005
Nocturnal dipping					
SBP dipping, %	11.2 ± 4.7	11.5 ± 5.7	10.6 ± 5.6	8.1 ± 5.6	.038
DBP dipping, %	18.8 ± 5.9	16.6 ± 7.7	17.0 ± 5.6	15.0 ± 7.7	.021
MAP dipping, %	13.8 ± 4.4	12.9 ± 6.2	12.5 ± 5.0	10.5 ± 6.5*	.013
SBP nondipper, n (%)	28 (50.0)	18 (39.1)	23 (37.1)	15 (57.7)	.93
DBP nondipper, n (%)	3 (5.4)	9 (19.6)	8 (12.9)	5 (19.2)	.13
MAP nondipper, n (%)	11 (19.6)	13 (28.3)	20 (32.3)	11 (42.3)	.029

Data are expressed as mean ± SD for parametric data and as number (%) for categorical data.
*Tukey honestly significant difference (HSD) test, $P < .05$, significantly different from nonsnoring healthy controls.
†Tukey HSD test, $P < .01$, significantly different from nonsnoring healthy controls.
‡Tukey HSD test, $P < .001$, significantly different from nonsnoring healthy controls.
§Fisher exact test, $P < .005$, significantly different from nonsnoring healthy controls.

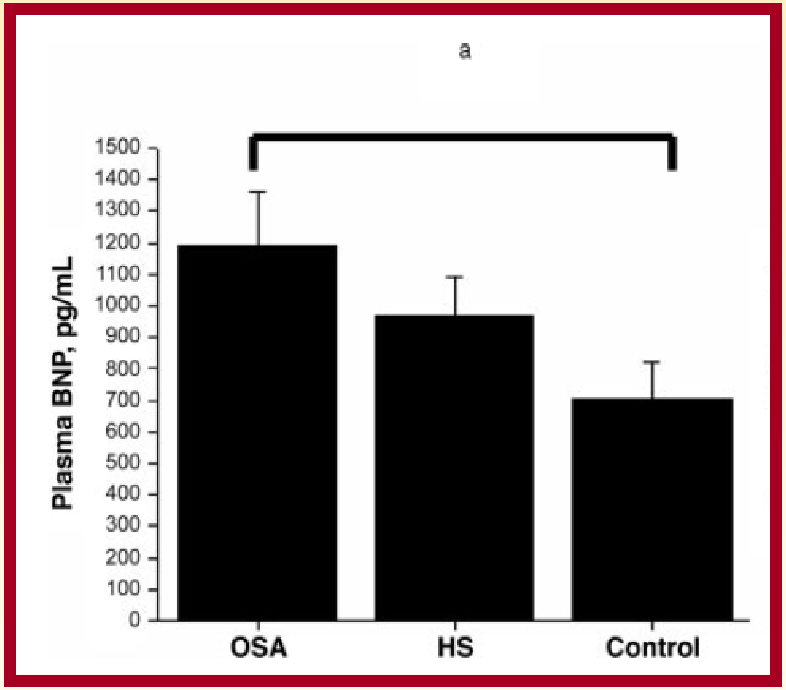
ORIGINAL ARTICLES
www.jpeds.com • The Journal of Pediatrics

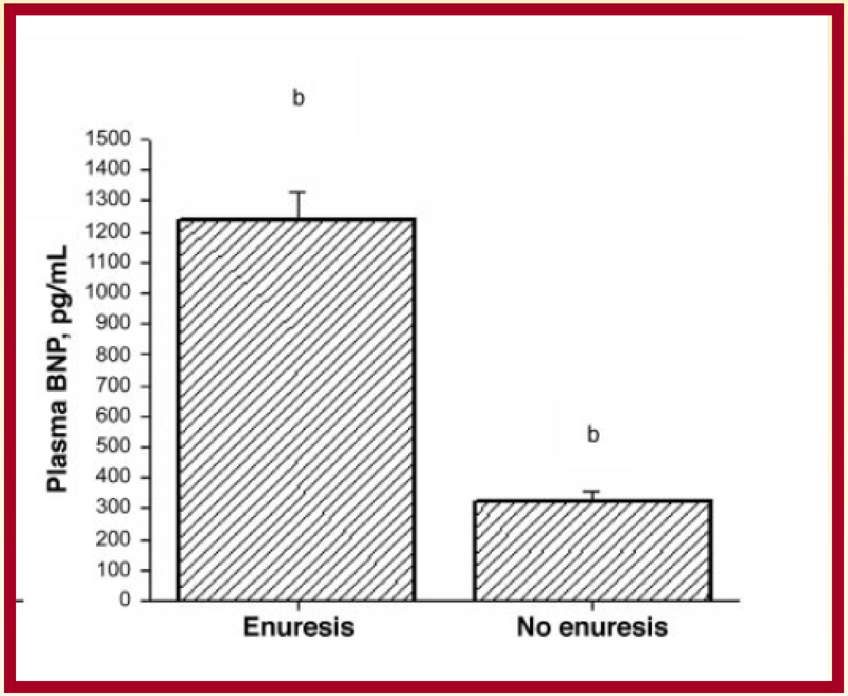
Blood Pressure is Elevated in Children with Primary Snoring

Albert M. Li, MD, Chun T. Au, MPhil, Crover Ho, RPSGT, Tai F. Fok, MD, and Yun K. Wing, MB

PS and Enuresis

Brain natriuretic peptide levels

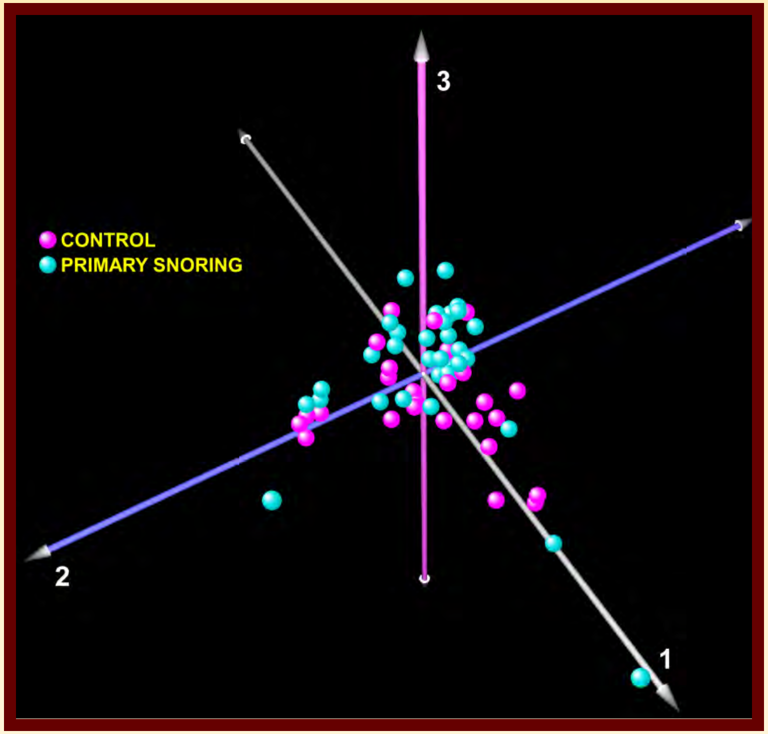




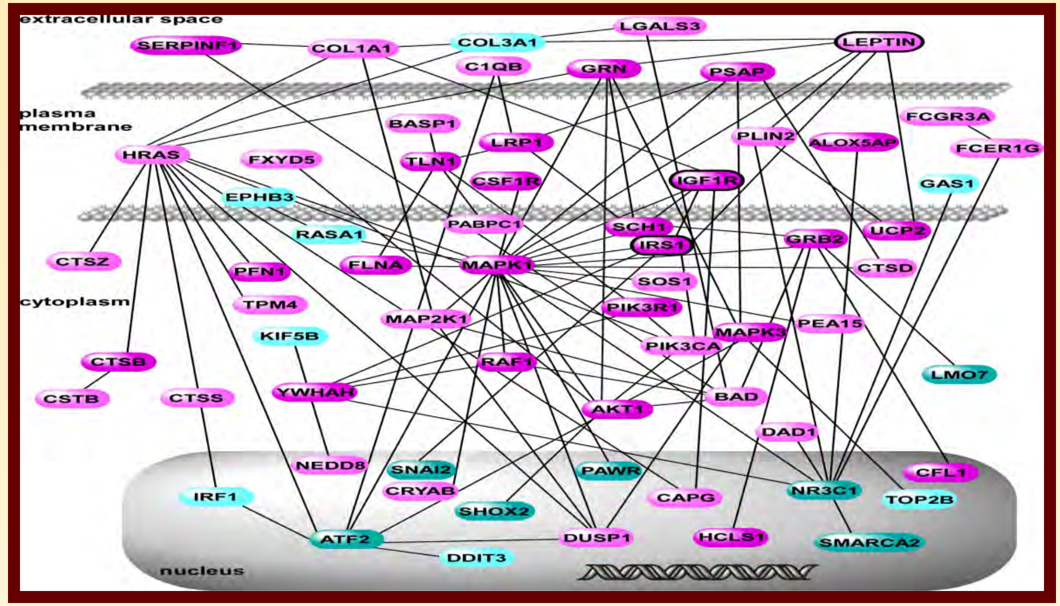
n=20/group
Matched for age, sex, BMI and enuresis

Sans Capdevila O et al. Pediatrics 2008

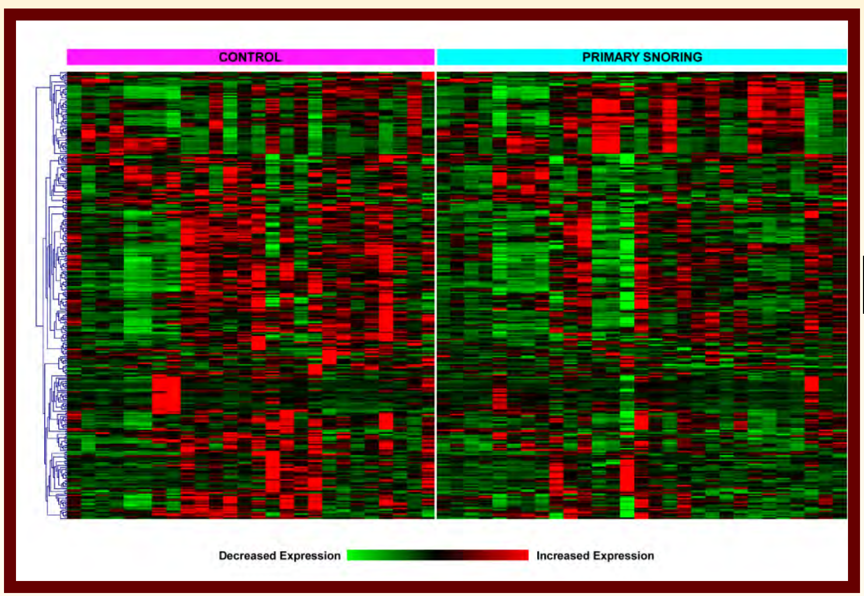
PS vs. CO



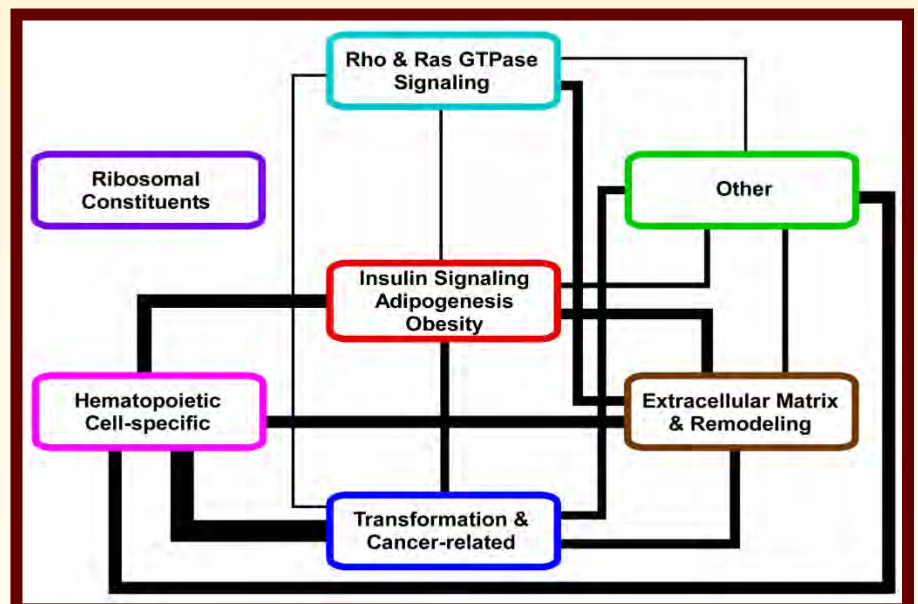
CONTROL
PRIMARY SNORING
3
2
1



extracellular space
SERPINF1
COL1A1
COL3A1
LGALS3
LEPTIN
C1QB
GRN
PSAP
plasma membrane
FCGR3A
FCER1G
BASP1
LRP1
PLIN2
ALOX5AP
HRAS
FXYD5
TLN1
CSF1R
IGF1R
GAS1
EPHB3
PABPC1
SCH1
UCP2
RASA1
IRS1
GRB2
CTSZ
PFN1
FLNA
MAPK1
CTSD
SOS1
cytoplasm
TPM4
MAP2K1
PIK3R1
PEA15
MAPK3
KIF5B
PIK3CA
CTSB
RAF1
LMO7
CSTB
CTSS
YWHAH
BAD
AKT1
DAD1
NEDD8
SNAI2
PAWR
CFL1
CRYAB
IRF1
CAPG
NR3C1
TOP2B
SHOX2
ATF2
DUSP1
HCLS1
SMARCA2
DDIT3
nucleus



CONTROL
PRIMARY SNORING
Decreased Expression
Increased Expression



Rho & Ras GTPase Signaling
Ribosomal Constituents
Other
Insulin Signaling Adipogenesis Obesity
Hematopoietic Cell-specific
Extracellular Matrix & Remodeling
Transformation & Cancer-related

Polysomnographic and metabolic characteristics of the second follow-up cohort

	PS (n=87)	**Control (n=65)**	***P*-value**
Glucose (mg/dl)	78.8±2.4	78.5±1.75	NS
Insulin (µIU/ml)	***8.3±1.30***	***6.1±0.72***	***<0.04***
HOMA-IR	***2.2±0.5***	***1.2±0.2***	***<0.04***
Triglycerides (mg/dl)	75.9±4.8	70.0±3.61	NS
Cholesterol (mg/dl)	168.1±3.9	161.9±3.5	NS
HDL (mg/dl)	55.5±1.6	52.2±1.2	NS
LDL (mg/dl)	97.4±2.9	93.7±3.0	NS
hsCRP (mg/l)	2.1±0.7	1.2±0.3	NS
SpO_2 nadir (%)	90.7±0.5	91.8±0.5	NS
Mean SpO_2 (%)	97.3±0.1	97.5±0.1	NS
Total arousal index (/hr TST)	14.3±1.3	13.3±1.0	NS
OAHI (/hr TST)	0.8±0.1	0.4±0.1	<0.01
BMI z-score	1.0±0.2	0.9±0.1	NS
Age (years)	6.7±0.2	6.8±0.3	NS
Male (n)	45	32	NS
African American (n)	22	16	NS

Summary

PS is associated with increased risk for neurocognitive and behavioral disturbances, increased cardiovascular risk, increased risk for enuresis, and increased risk for insulin resistance

Based on these findings,

we should treat all children

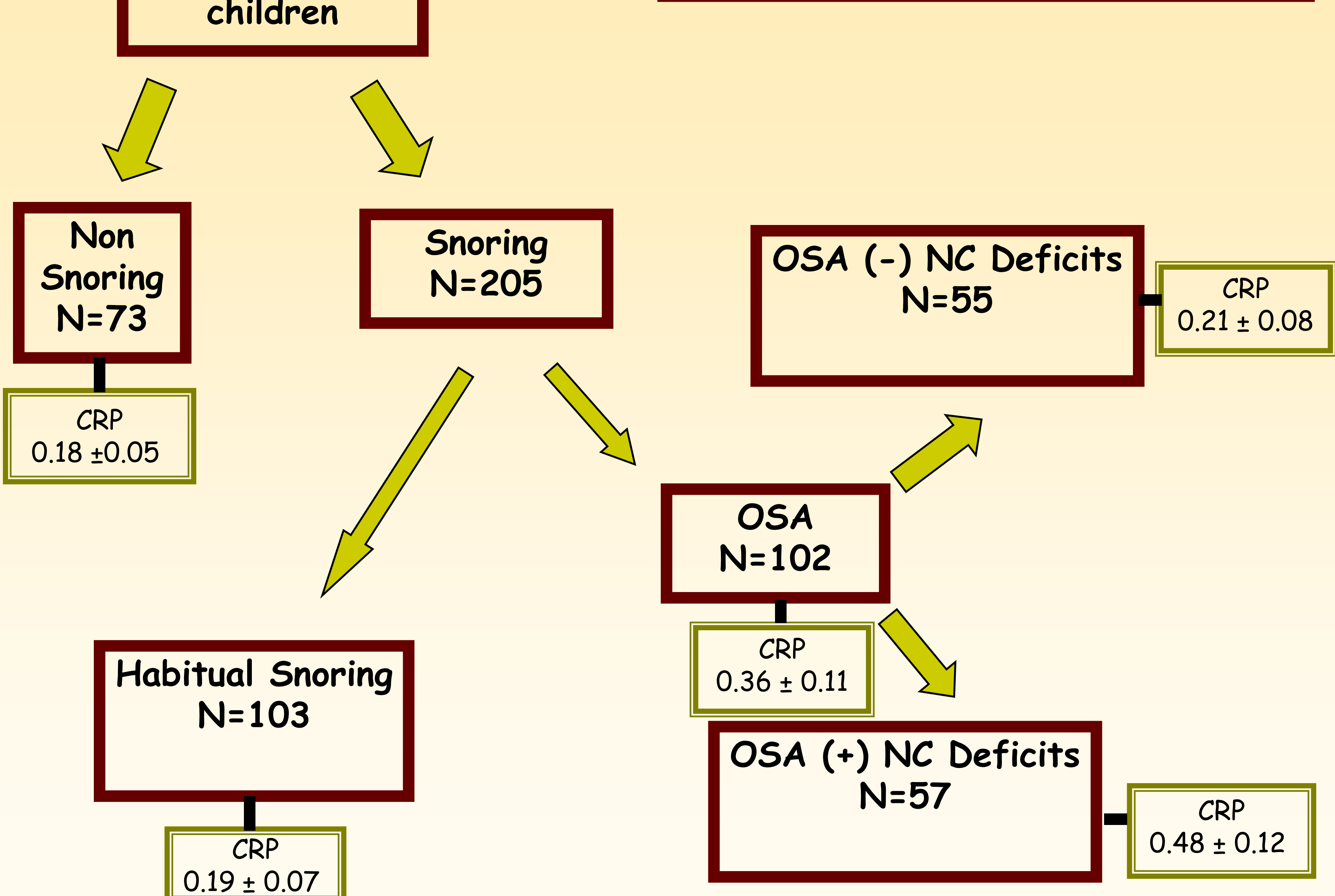
with primary snoring, in that case

sleep studies would not be needed!!!

Problem II

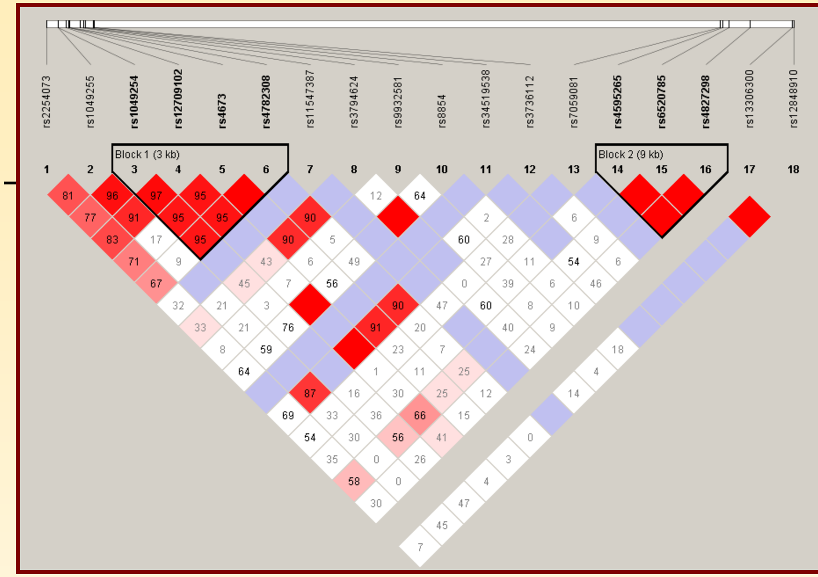
At any given level of OSA severity based on polysomnographic measures, there are children with neurocognitive deficits and otherwise age, gender, ethnicity, maternal education, and BMI-matched children who do not have neurocognitive deficits!

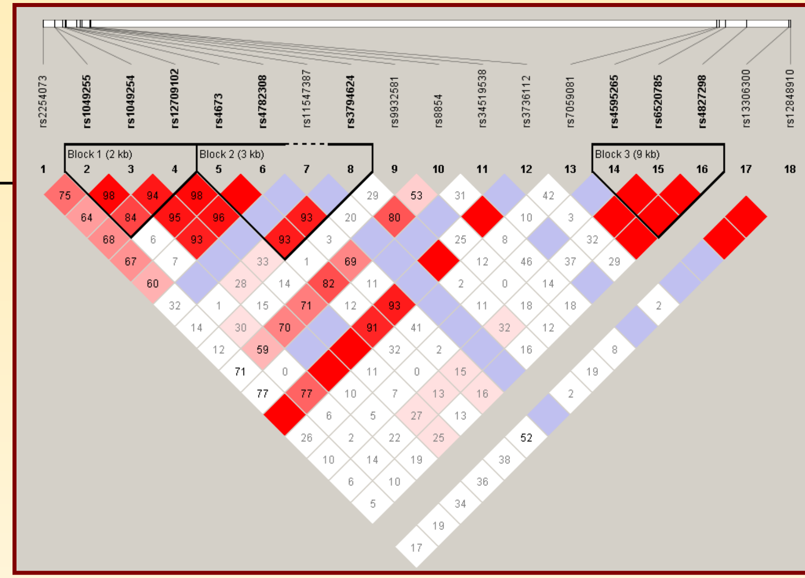
CRP and Cognitive Function in Children
Gozal et al., AJRCCM 2007

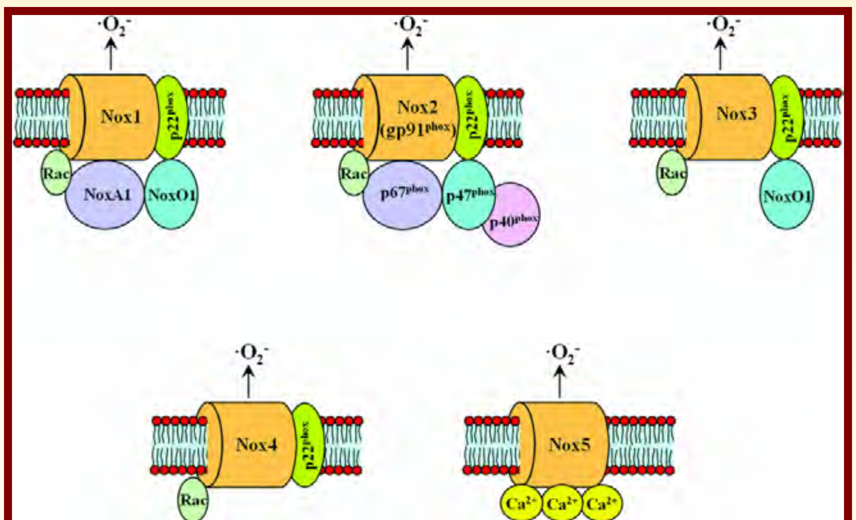


Control

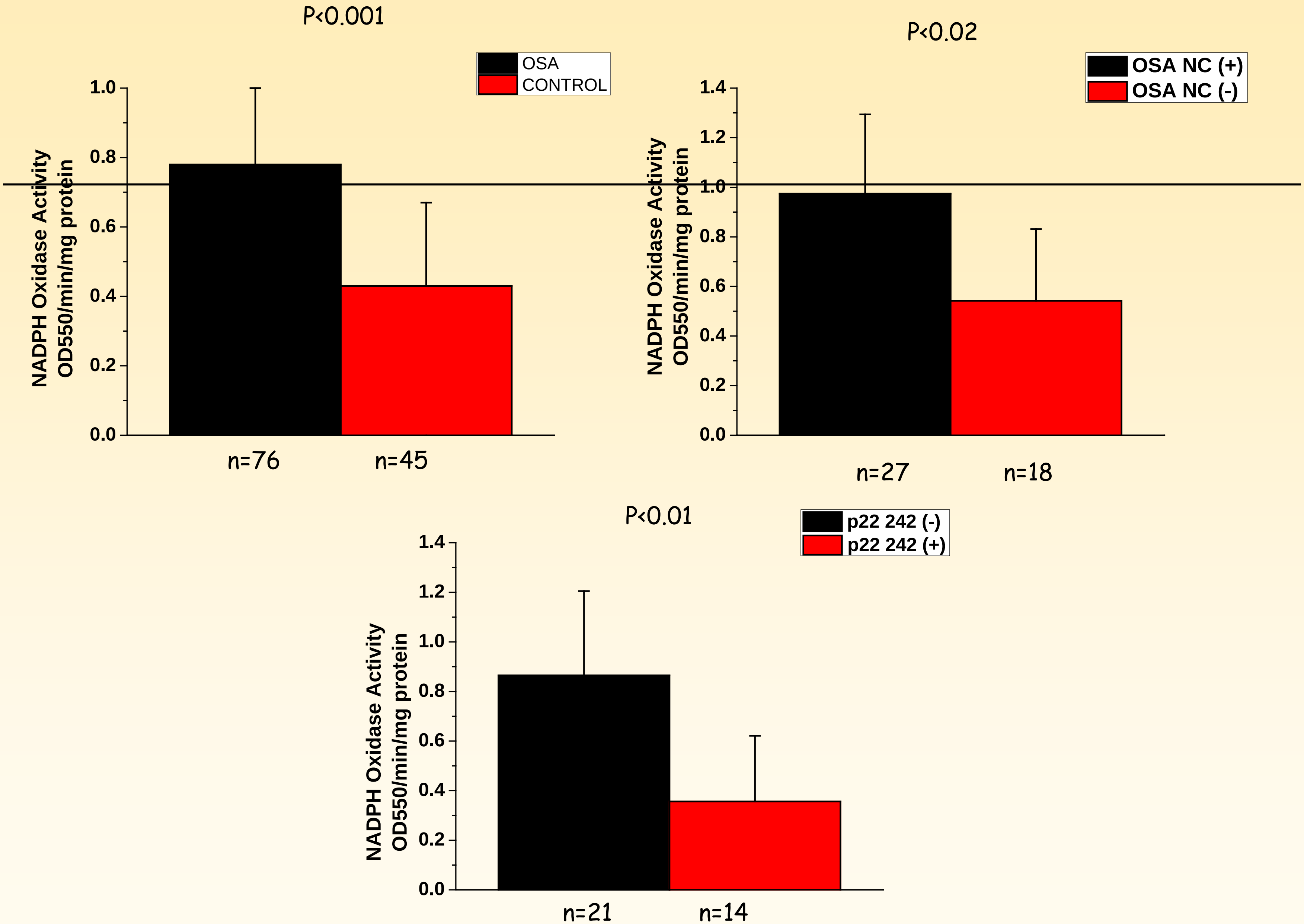
OSA







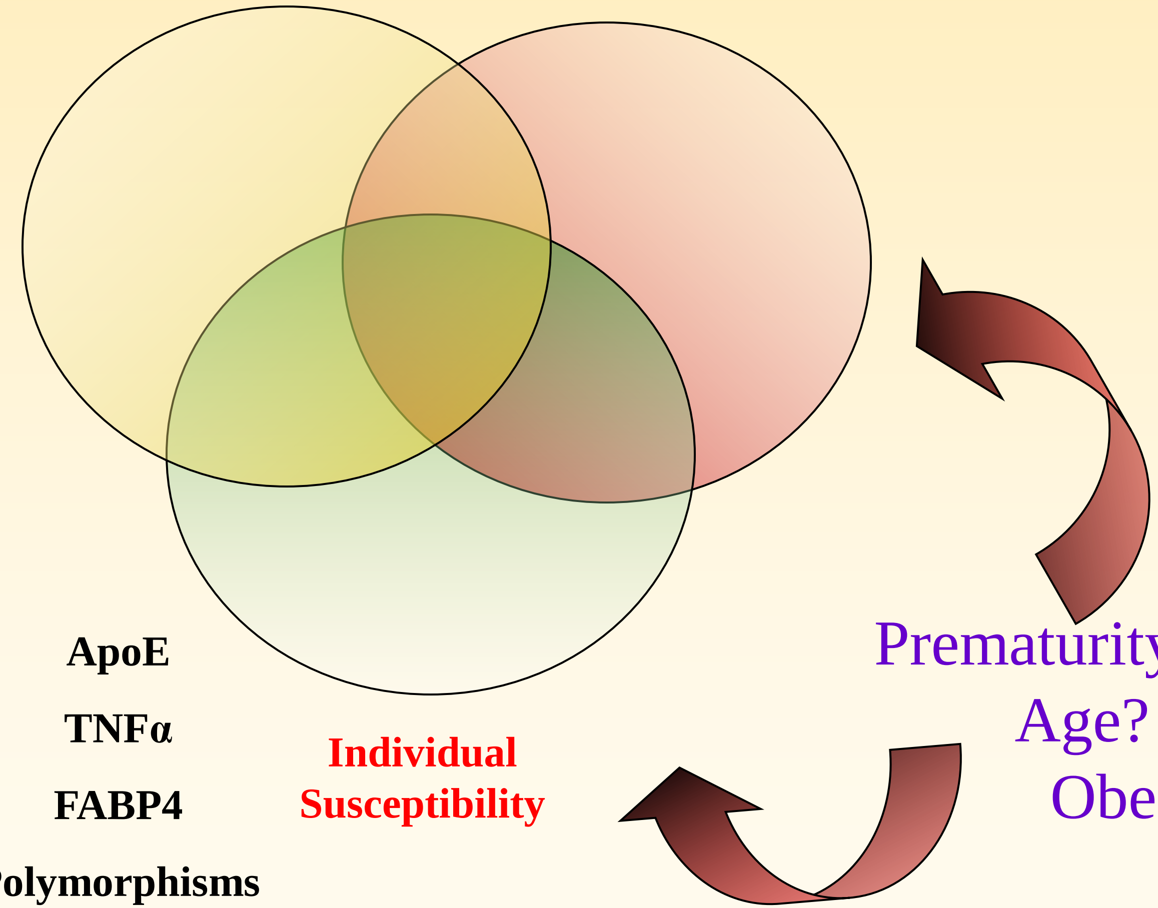
Gozal et al, Antioxidants Redox Signal. 2012



Gozal et al, Antioxidants Redox Signal. 2012

Triple Risk SDB Morbidity Model

Environment **SDB Severity**



Food

Exercise

Pollution

Literacy

ApoE

TNFα

FABP4

Polymorphisms

Individual Susceptibility

Prematurity?

Age?

Obesity?

Gozal & Kheirandish, 2006

Problem III

Some children not fulfilling statistical criteria for "disease" may be symptomatic and display measurable morbidity while other children who fulfill statistical criteria for "disease" may not exhibit end-organ morbidity. Should we treat a snoring child if ***no evidence*** *of damage is present?*