**Sleep in Autism Spectrum Disorders:
Window to Treatment and Etiology**

Ruth O'Hara, Ph.D.

Associate Professor,
Department of Psychiatry and
Behavioral Sciences,
Stanford University School of
Medicine

Disclosures

- **NONE**

Acknowledgements

Sleep Disturbances in ASD:
A Substantial Concern for Parents

- Multiple Studies of Parental Reports Suggest Sleep Disturbances common in ASD

- Main Parental complaints:
  - **44%** sleep initiation difficulties
  - **31%** sleep maintenance difficulties
  - **30%** early morning awakening

- Prevalence Rates of Subjective Reports Range from 44-86%

  (Richdale 1995, Schreck 2000, Goodlin-Jones 2002, Wiggs 2004, Couturier 2005, Allik 2006, Krakowiak 2008)

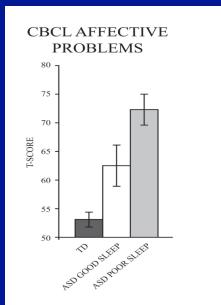## Association of Sleep Disturbances with
ASD Core Symptoms

CBCL AFFECTIVE PROBLEMS

- More affective problems in children with ASD who are poor sleepers *(Malow, 2006)*

- Association between sleep onset disturbance and communication impairments in low functioning ASD *(Quine, 1991)*

- Association between total sleep time and non-verbal communication *(Richdale, 2009)*

Why should we care about Sleep in Autism?

- Sleep disturbance impacts cognition, mood and behavior
- Negative impact on health and well-being of the family
- Sleep Disturbances can reflect many Sleep Disorders
- Many Sleep Disorders can be treated
- Characterizing Sleep Dysregulation in ASD may
  - Indentify valuable biomarkers
  - Provide a window to etiology
  - Refine our phenotypes

What Do We Know about Sleep in ASD?

- **Limited Number of Studies**

- **Different Assessment Methodologies Employed**
  - **Sleep Diaries**
  - **Actigraphy Measures of Activity**
  - **Video Recordings**
  - **Full Polysomnography (PSG): Gold Standard Assessment of Sleep**

- **Sleep Studies of ASD employ Sleep diaries and Actigraphy**

Do Objective Sleep Assessments Validate Parental Observations?

Objective Sleep Disturbances in ASD

	AUT (n = 68)	DD (n = 57)	TYP (n = 69)
Bedtime	21:00 (1:08)	21:07 (1:00)	20:46 (0:51)
Sleep start	21:36 (1:13)	21:46 (1:13)	21:19 (0:53)
Sleep end	6:58 (0:57)	7:24 (1:02)	7:11 (0:40)
Time in bed	9:57 (0:53)	10:13 (0:48)	10:25 (0:35)
% Sleep	97.1 (2.5)	95.4 (3.5)	97.2 (1.8)
Sleep-onset latency time[a]	0:39 (0:28)	0:42 (0:31)	0:35 (0:19)
WASO duration[a]	0:18 (0:16)	0:29 (0:22)	0:18 (0:12)
WASO no.[b]	2.5 (1.7)	3.7 (2.4)	3.1 (1.8)
Sleep efficiency	91.3% (4.6)	89.7% (5.1)	91.8% (3.5)
24-hour sleep	10:36 (0:51)	11:06 (0:54)	11:14 (0:43)
Nappers (n = 164)	AUT (n = 54)	DD (n = 48)	TYP (n = 62)
Nap duration[a]	0:47 (0:58)	0:58 (1:00)	0:54 (0:58)
No. of naps[b]	0.65 (0.76)	0.65 (0.48)	0.66 (0.45)

Decreased sleep duration over 24h

Goodlin-Jones, J Am Ac Child & Adolesc Pychiatry 2008

Full PSG Assessment of Sleep in ASD is Rare

- Sleep Diaries, Actigraphy and Videos are valuable but limited as they **Do Not** Assess Sleep Architecture

- Capture sleep initiation **BUT NOT** sleep maintenance difficulties

- Equate lack of movement with sleep but cannot capture micro-arousals in sleep

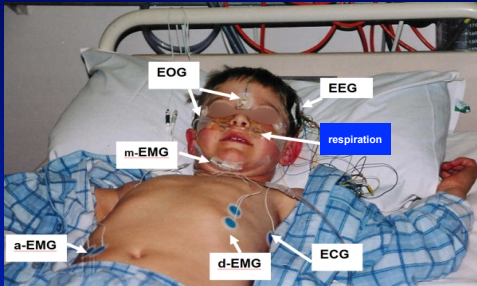## Objective Sleep Assessment: Overnight Lab/Clinic Polysomnography

Buckley (2010) Arch Ped Adol Med: Polysomnography Validates Parental Report

Children With Autism Have Shorter Total Sleep Time, Increased SWS, and REM Sleep Deficiency

	Autism (60)	Typical (15)	DD (13)	P value
Age, y	4.49 (1.95)	3.60 (2.42)	3.91 (1.44)	.38
Range	2-13y	1-6y	2-7y	
Total sleep time, h	7.70 (2.04)	8.83 (1.66)	9.15 (1.14)	.004
Latency to sleep, min	28.5 (65.5)	37.5 (34.5)	33.0 (11.5)	.29
Sleep efficiency, %	83.7 (16.5)	86.2 (11.8)	87.8 (8.9)	.29
WASO, min	50.1 (82.7)	37.0 (40.0)	45.1 (43.8)	.02
Stage 1 sleep, %	4.7 (4.9)	3.7 (1.2)	2.1 (2.3)	.14
Stage 2 sleep, %	56.4 (12.3)	55.8 (8.5)	57.3 (10.7)	.62
Stage 3 SWS sleep, %	21.5 (9.0)	18.6 (5.4)	13.7 (7.1)	.001
REM sleep, %	14.5 (8.4)	22.6 (6.5)	25.0 (6.8) .	.001
REM sleep latency, min	108.5 (80.3)	64.0 (59.0)	69.0 (27.5)	.02

Limitations of Overnight Laboratory Approaches

- Limited ecological validity

- Sample bias

- Do not Assess for Sleep Disorders

- Difficult for Patients with ASD

- One Night Effect

Sleep Disturbance Can Reflect Very Different Sleep Disorders

- Sleep Disturbance Can Reflect Very Different Sleep Disorders
  - Sleep Disordered Breathing e.g. Sleep Apnea, hypoventilation
  - Insomnia
  - Circadian Rhythm Disorder
  - Restless Legs Syndrome
  - Periodic Limb Movements
  - Rapid Eye Movement Sleep Disorder
  - Sleep Terrors

- Effective Treatments Exist for Many Sleep Disorders

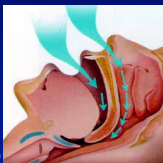- Systematic Consideration of Sleep Disorders in ASD is minimal

---

What Do we Know About Sleep Disorders in ASD?
Knowledge on Sleep Disordered Breathing is Minimal

- Apnea = cessation of respiration

- Hypopnea = partial decrease (>50%) of respiration

- Duration ≥10 seconds

- Apnea/Hypopnea Index ≥5/h of sleep

Sleep Apnea Case Studies in ASD

- Gozal et al, 2008 Pediatrics
    - Prevalence of Sleep Apnea in Typical Developing Children as high as 30%
    - Impaired School Functioning
    - Increased daytime sleepiness and napping

- Gozal et al, 2010 Pediatrics

    - Case Study of Child with ASD: Improved Following Treatment
    - Impaired cognitive function and auditory processing
    - Impaired Endothelial function
    - Increased inflammation (TNF-a)

- Malow et al., 2004, Sleep
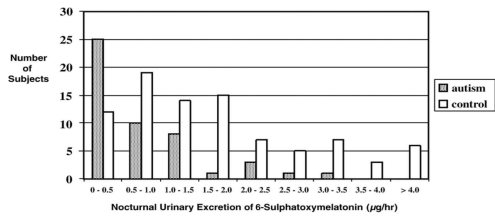   - One Case Study of Child with ASD with Apnea: Improved Following Treatment

---

Circadian Rhythms Are Dysregulated in ASD:
May Reflect Reduced Melatonin Synthesis in ASD

Nocturnal urinary 6-SMT rate ↓ in 49 ASD children (12y±5) vs. 88 matched NT ctrls *(Tordjman, 2005)*

Number of Subjects — Nocturnal Urinary Excretion of 6-Sulphatoxymelatonin (μg/hr)

Legend: autism, control

- 63% had $<\frac{1}{2}$ nocturnal melatonin excretion rate than controls

---

Restless Legs Syndrome and ASD:
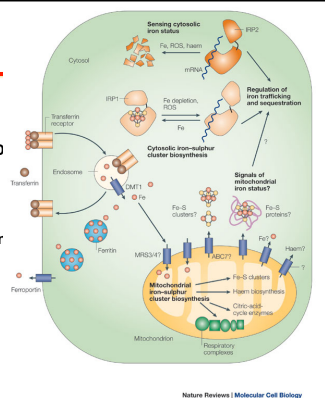
- Iron Deficiency key in RLS
- Iron Deficiency identified in ASD
- RLS may be a significant sleep disorder in ASD
- RLS leads to significant sleep fragmentation and dysregulation
- May impact core cognitive and behavioral symptoms in ASD

Nature Reviews | **Molecular Cell Biology**

Simons Foundation Grant:
Characterization of Sleep Disorders in ASD

- To describe the range and type of sleep disorders experienced in individuals with ASD (n=80).

- To examine the impact of the type and severity of sleep disorders on the cognitive and behavioral symptoms in these individuals with ASD.

- To examine for specific patterns of impaired sleep architecture in ASD relative to controls, which have the potential (a) to serve as biomarkers of this disorder, and/or (b) to define specific phenotypes or subgroups.

Sleep Assessment with
Ambulatory In-Home Polysomnography

- Electroencephalogram (EEG)
- Electroocculogram (EOG)
- Submental Electromyogram (EMG)
- Nasal airway pressure
- Nasal/oral airflow
- Finger Pulse Oximetry
- Snoring
- Movements of rib cage and abdomen
- ECG
- Body position

Pediatric Fully Ambulatory Polysomnography

Pediatric Full Ambulatory Polysomnography

After you will go to sleep with all the sensors on

Sleep Recording Output from Polysomnography

Systematic Behavioral Desensitization

- Initial visit to the home to do the consent and assent

- Bring a booklet on the process to read with the child

- On a second visit we bring non-working equipment –

  - EEG cap

  - electrode leads

  - Cannula (to assess for sleep disordered breathing)

- Child wears equipment and places it on the Sleep technician

- Leave equipment in home for wearing at night until family feels child is ready for PSG

- This process typically takes 2-4 weeks per child assessed

Study Progress to Date

- 105 subjects consented and enrolled in the investigation

  - 75 ASD subjects assessed to date with full ambulatory PSG

  - 10 Siblings assessed to date with full ambulatory PSG

  - 30 healthy, historical controls from Stanford Sleep Center

---

O'Hara et al: Sleep Polysomnography Findings

	Autism	Sibs	Controls	P value
Age, y	9.65 (3.95)	10.60 (2.72)	10.91 (2.44)	.40
Range	3-15y	6-15y	3-15y	
	17M/3F	8M/2F	17M/3F	
Total sleep time, h	6.20 (2.16)	7.71 (2.20)	8.25 (3.30)	.01
Latency to sleep, min	24.33 (29.2)	17.5 (19.45)	23.0 (11.5)	.33
Sleep efficiency, %	72 (25.2)	89.1 (10.1)	86.6 (10.)	.06
WASO, min	19.7 (21.3)	25.9 (16.0)	40.1 (20.1)	.01
Stage 1 sleep, %	3.6 (5.45)	2.7 (1.4)	2.0 (2.2)	.20
Stage 2 sleep, %	38.4 (16.1)	45.2 (9.5)	52.3 (12.3)	.22
Stage 3 SWS sleep, %	45.48 (9.0)	30.1 (9.3)	23.4 (8.2)	.001
REM sleep, %	12.5 (6.4)	24.2 (8.1)	25.0 (9.1) .	.001
REM sleep latency, min	118.1 (64.3)	85.0 (51.0)	70.0 (22.8)	.01

O'Hara et al: Sleep Disorders Findings

	Autism (75)	Sibs (10)	Controls (30)	P value
Age, y	9.65 (3.95)	10.60 (2.72)	10.91 (2.44)	.40
Range	3-15y	6-15y	3-15y	
Sleep Apnea %	40%	20%	10%	.01
AHI$\leq$ 3 hr	3.8 (2-5.5)	1.2 (1-5)	.70 (1-7)	.05
AvSaO2	96%	98%	97%	.40
MinSaO2	91%	95%	95%	.05
Insomnia	55%	40%	25%	.001
Periodic Limb Movement	25%	15%	15%	.10
PLM	4.42 (0-40.8)	.70 (0-5)		.01
Spontaneous Arousals	10.29 (0-21)	5.25 (0-6)		

Causes of Sleep Disturbances in Children with ASD

- **Coexisting Medical Disorders**
  - **Neurological disorder (e.g. epilepsy),**
  - **Medical disorder (e.g. GI reflux, Sinus) or psychiatric comorbidity (e.g. anxiety, depression)**

- **Medications**
  - **Corticosteriods, bronchodialators, psychiatric medications**

- **Neurobiological**
  - **GABA, 5-HT (Serotonin), Melatonin**

- **Behavioral and Environmental**
  - **Inadequate Sleep Hygiene**
  - **Excessive light at night, excess noise, bedroom too warm, too cold**
  - **Agitation from the experiences of the day, school problems, frustration**

Sleep disorders Provide Treatment Opportunities for Autism Spectrum Disorders

- **Insomnia**
  - **Behavioral therapies, including attention to daytime habits, bedtime routine, and interactions with caregivers during night**
  - **Supplemental melatonin**
  - **Light therapy**

- **Obstructive sleep apnea**
  - **Weight loss**
  - **Continuous positive airway pressure**

- **REM behavior disorder**
  - **clonazepam (first line), dopaminergic agents, melatonin, and home safety measures**

- **Periodic limb movements of sleep and/or Restless Leg Syndrome:**
  - **dopaminergic agents (first line)**
  - **Ferritin or Iron Supplementation**

Sleep disorders Provide Clues to the Biomarkers and Phenotyping of ASD

- Insomnia
  - Melatonin deficiency

- Sleep apnea
  - Hypoxia during neuronal development
  - Serotonergic deficiencies
  - SCN deficiencies or dysregulation
  - Cardiac dysregulation
  - Immune dysfunction

- REM deficiency
  - Neurotransmitter deficiencies
  - Impaired neuronal development
  - Circadian Rhythm Disorder

- Periodic limb movements of sleep and/or Restless Legs Syndrome
  - dopaminergic deficiencies
  - Ferritin deficiencies

Conclusions

- Data suggests Sleep Dysregulation and Sleep Disorders are very common ASD
  - Neuroscience of Normal Sleep
  - Circadian Rhythms
  - Sleep Disorders
- Sleep Disorders Represent an Important opportunity for therapeutic interventions
  - Mind and Body Relationships
  - Body and Mind Relationships
- Increased Characterization of Sleep Architecture may serve as a valuable biomarker in ASD, point to etiological basis and/or provide for phenotypic refinement

Future Directions

- Increased Characterization of Sleep Disturbances in ASD
- Increased knowledge of the prevalence of sleep disorders
- Detailed sleep architecture and EEG measures of sleep deprivation
- Investigation of the shared neurobiological factors implicated in both sleep-wake regulation and ASD
- Neurodevelopmental consequences of early-on sleep disturbance, disorders and circadian rhythm disturbances requiring longitudinal approaches

11