REGRESSION IN PMS AND SLEEP DISTURBANCES IN PMS

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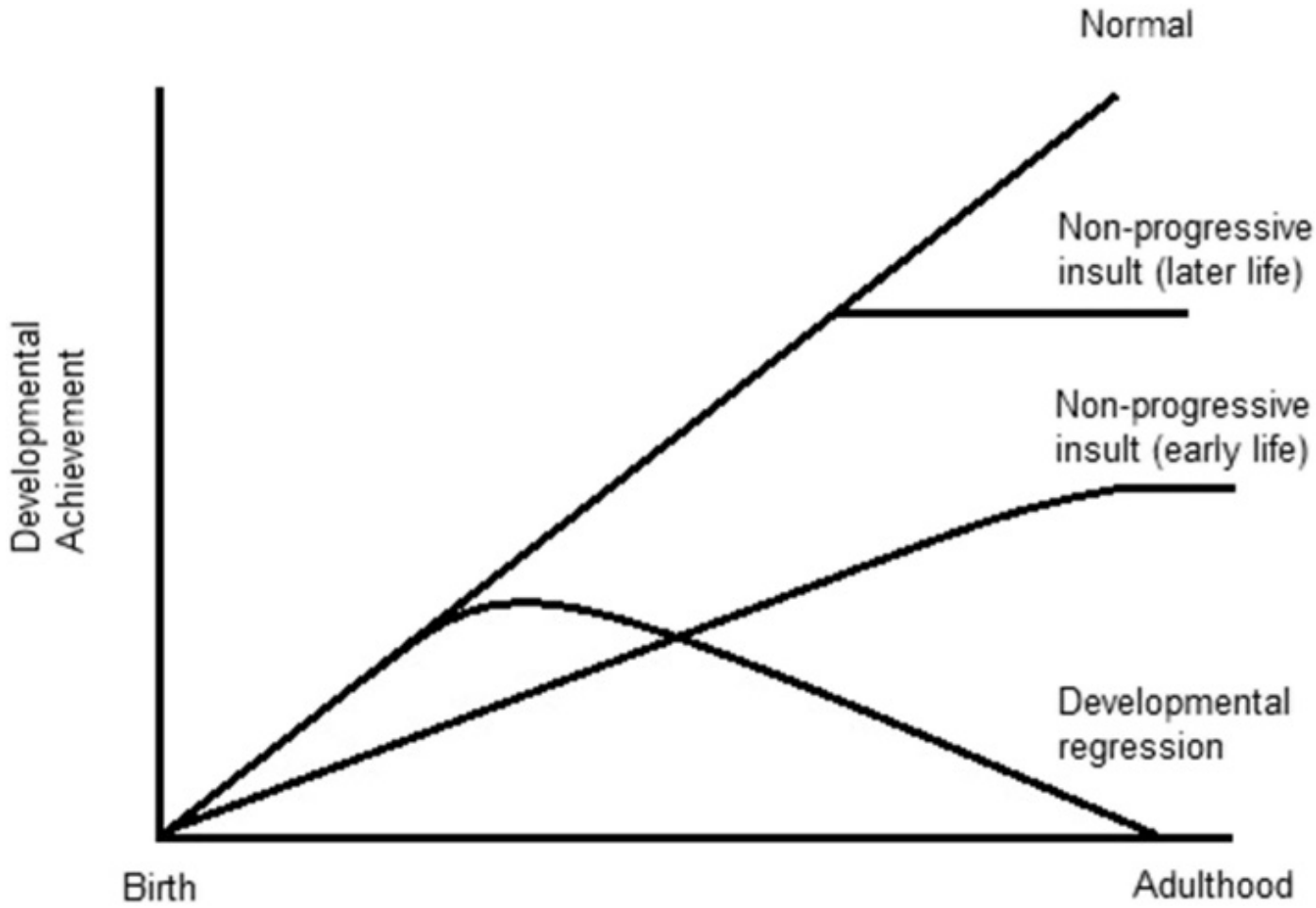
THE PHELAN-MCDERMID SYNDROME FOUNDATION INTERNATIONAL REGISTRY

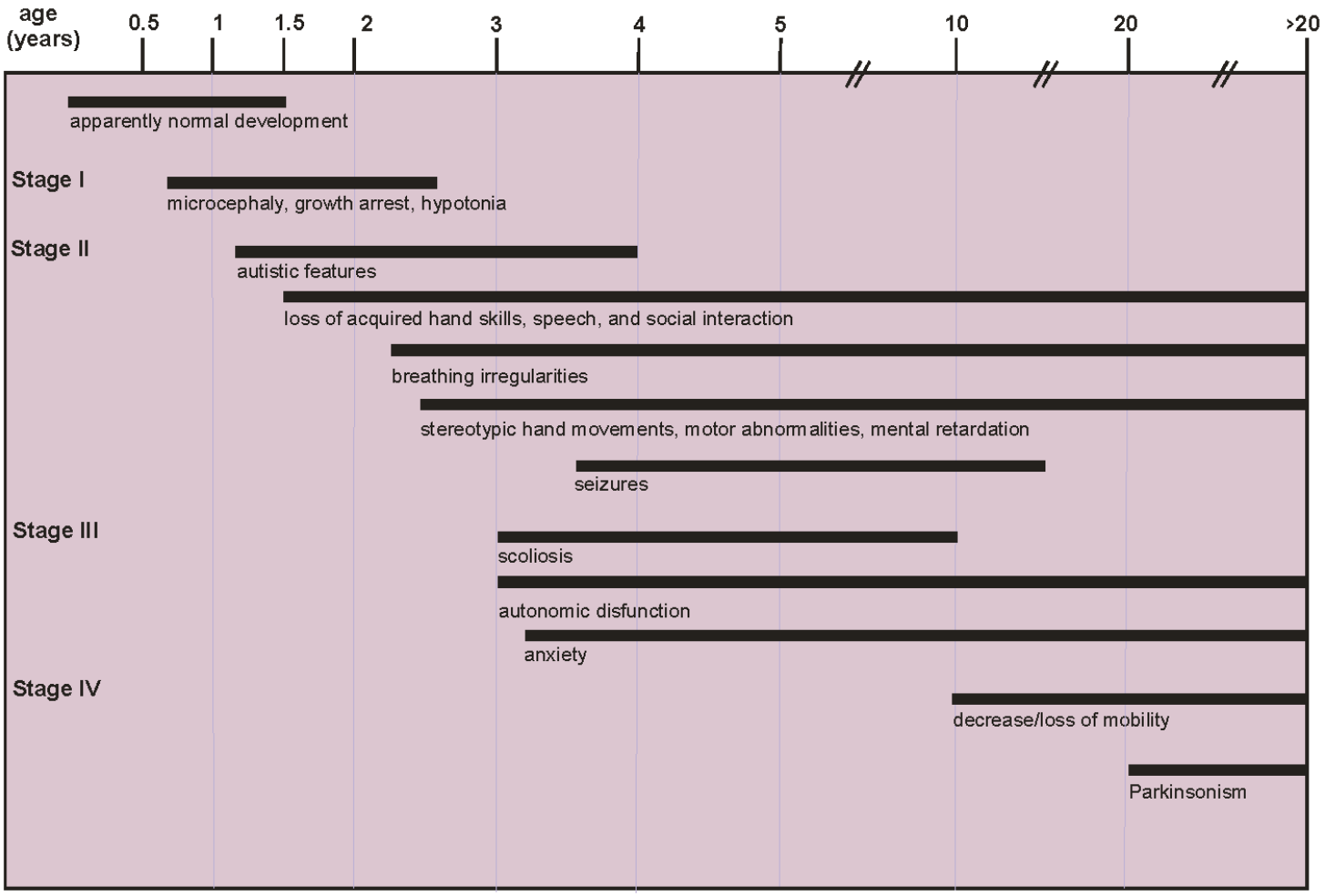
Regression

- Loss of already acquired skills
  - Person who had previously exhibited normal development progressively loses key 'milestones' they have acquired
  - Example:
    - Child walks at 14 months, at 4 years becomes unable to walk, then unable to crawl and so on
  - Contrast:
    - Delay: Failure to achieve key abilities

Developmental Trajectories



Regression in Rett Syndrome



Regression in Autism Spectrum Disorder (ASD)

- Occurrence of reported regression is higher in ASD than other idiopathic developmental conditions
- Mainly Language and Social Skills
- Meta-analytic review (Barger et al., 2013)
  - 85 studies (n = 29 035)
  - Overall prevalence of regression in ASD to be 32.1% (confidence interval (CI): 29.5–34.8)
  - Mean age of onset of regression as 1.78 years (CI: 1.69–1.89).[10]

Regression in PMS

- Three Case Reports
  - Regression affects motor and language skills
- Wilson et al. (2003)
  - Survey of parents
  - 17/48 or 35% reported history of loss of skills
  - No description of age of onset or type of skill loss
- Dhar et al. (2010)
  - 2/23 (15%) experienced regression

Regression in PMS

- Soorya et al. (2013)
  - ADI-R
  - 28% were identified as having loss of skills
  - Most commonly language
  - 5/9 language loss associated with epilepsy

Regression in PMS

- Studies suggested Regression is impacted by
  - Deletion size
  - Epilepsy

Regression in PMS - Sample

- Recruitment through letters and e-mails
  - Participants of ongoing research studies,
  - Lucile Packard Children's Hospital
  - Interest groups for patients and families with genetic disorders associated with ASD
- Assessments
  - Stanford Binet Intelligence Scales 5th edition
  - Mullen Scales of Early Learning
  - Autism Diagnostic Interview Revised (ADI-R)

Sample – Regression Study

	n	%
Age (in years) n = 50		
0–6	9	18
>6-12	21	42
>12-18	11	22
>18	9	18
Sex (n = 50)		
M	25	50
F	25	50

Non Verbal IQ – Regression Study

NVIQ	%
<35	59
35–49	28
50–70	9
>70	3

Regression – Assessment

- Autism Diagnostic Interview-Revised (ADI-R)
  - Tool to assist in characterizing regression
  - Includes specific questions and guidance about regression
  - The characteristics required for language regression
    - Prior to the reported loss, 'communicative use of at least five different words (other than "mama" and "dada") on a daily basis for at least 3 months' is established

      and

    - loss of the skill for at least 3 months (quoted from a test booklet of an assessment tool).

Regression – ADI Parameters

- Language Loss
  - At least 5 different words other than mama/dada for three months
- Purposive Hand Movements
  - Ability to grip/hold objects
- Motor Skills
  - Posture, Gait, and Coordination
- Self-help skills
  - Feeding, Dress, Using Bathrooms etc.
- Constructive or Imaginative Play
  - Puzzles, Games, Make-believe etc.
- Social Engagement and Responsiveness
  - Social Relatedness, Interest, and Involvement

Regression in PMS

Parents of 43% of Patients Reported a History of Regression

Regression – Motor Skills

Motor Skills	%
No loss	41
Some loss	0
Definite loss	59

Regression – Self Help Skills

Self help skills	%
No loss	41
Some loss	6
Definite loss	53

Regression – Language and Social Engagement

Language	%
No loss	86
Loss	14
Social engagement and responsiveness	%
No loss	65
Some loss	6
Definite loss	29

Regression – Purposive Hand Movements

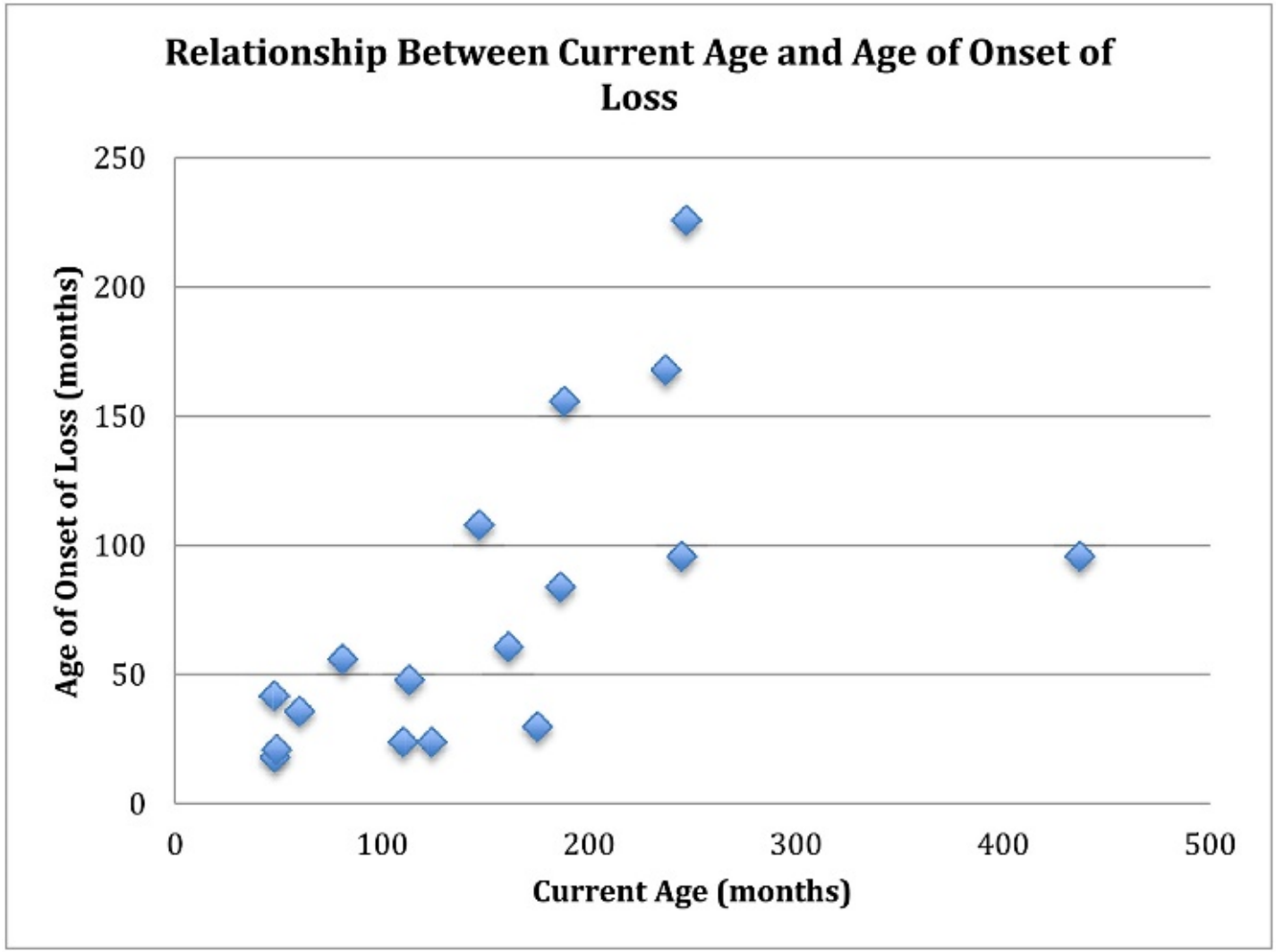
Purposive hand movements	%
No loss	65
Some loss	6
Definite loss	29

Regression – Constructive Play

Constructive or imaginative play	%
No loss	76
Some loss	0
Definite loss	24

Regression - Characteristics

ADI-R Skill Losszz	%	Males	Females	Mean age of loss (mo.)	Median age of loss (mo.)
Motor skills	56	5	5	95	90
Self-help skills	50	5	4	49	36
Language	33	2	4	39	40
Social engagement and responsiveness	33	4	2	63	63
Purposive hand movements	28	2	3	80	96
Constructive or imaginative play	22	1	3	48	30



Average Onset: 6 years (mean = 76 months, median = 56 months, range = 18 months to 18 years).

Regression and Seizure History

Seizure History (n = 35)	%
Negative	37
Positive	63
EEG (n = 35)	
Normal	29
Abnormal	71

Neither Seizures nor abnormal EEG significantly predicted regression

Regression in PMS

- 43% of patients experienced regression
  - Greater than previously reported
- Onset of regression
  - Mid-childhood – 6 years of age
  - Later then in ASD and Rett Syndrome
- Most commonly affected
  - Motor and self-help skills

Comparison to Soorya et al.

Variable	Current Study	Soorya et al. (2013)
Mean age (median) of all patients (years)	12.5 (9.9)	8.8 (6.5)
Mean age (median) of patients with regression (years)	12.7 (11.3)	n/r (n/r)
Mean age (median) of patients without regression (years)	12.3 (9.1)	n/r (n/r)
NVIQ <35 of all patients (%)	59.4	76.7
Mean NVIQ (median) of all patients	28.6 (19.9)	25.2 (19.4)
Mean NVIQ (median) patients with regression	19.4 (19)	n/r
Mean NVIQ (median) patients without regression	37.8 (42)	n/r
Mean (median) age of onset of skills regression (years)	6.3 (4.7)	n/r
Loss of skills (%)	43	28

Regression in PMS

- Neurodevelopmental Disorders have distinct patterns of regression
- PMS
  - High Rate of regression
  - Later than in other neurodevelopmental disorders
  - Neither seizures nor abnormal EEG predicted regression
  - Deletion size did not Predict Regression

Limitations

- Small sample size
- Retrospective
- Predominantly Caucasian

LARGER LONGITUDINAL STUDIES ARE NEEDED

Sleep and PMS

- Sleep disturbances are thought to be common in PMS – Significant Parental Complaints
- No systematic studies
- Primary Aims of Our Study
  - Document sleep disturbance in Individuals with PMS via Caregiver Report
  - Determine whether Individuals with PMS are evaluated for sleep disorders
  - Examine Relationship between sleep behavior of individual with PMS and the sleep behavior of their caregiver

Why should we care about Sleep in PMS?

- Sleep disturbance impacts cognition, mood and behavior
- Characterizing Sleep Dysregulation has the potential to
  - Identify biomarkers
  - Refine phenotypes
  - Point to etiological pathways
- Significant negative impact on health and well-being of the family
- Sleep Dysregulation and/or Sleep Disorders can be Treated

Sleep and PMS (Bro et al., SLEEP, 2017)

- Participants recruited through an e-mail sent by the PMSF to their members
  - Link to Online Survey
    - Children's Sleep Habit Questionnaire (CSHQ; Owens et al., 2000)
    - Parents' Sleep Habits Questionnaire for the Caregiver
  - Survey was available for the month of January 2015

Children's Sleep Habit Questionnaire

- Each item is rated on a scale from 1 to 3
- 33 items grouped into 8 subscales
  - Bedtime resistance
  - Sleep onset delay
  - Sleep duration
  - Sleep anxiety
  - Night awakenings
  - Parasomnias
  - Sleep disordered breathing (SDB)
  - Daytime sleepiness
- Yields Total Sleep Disturbance Score
- Additional Questions asked if individual with PMS had an Objective Sleep Assessment or Sleep Disorder Diagnosis
- Parents' Sleep Habit Questionnaire covers same domains and uses same format

Children's Sleep Habit Questionnaire

	1 Usually (5-7)	2 Sometimes (2-4)	3 Rarely (0-1)	Problem?
1. Child goes to bed at the same time at night	□	□	□	Yes No N/A
2. Child falls asleep alone in own bed	□	□	□	Yes No N/A
3. Child falls asleep within 20 minutes after going to bed	□	□	□	Yes No N/A
4. Child sleeps the right amount	□	□	□	Yes No N/A
5. Child sleeps about the same amount each day	□	□	□	Yes No N/A
6. Child wakes up by him/herself	□	□	□	Yes No N/A

Higher Score = Worse Sleep (Range 31 to 93; $\geq$ 41 Clinically Significant)

Demographics – Caregivers

Gender (n = 193)	
Male	14.5%
Female	85.5%
Age group (years)	
21–30	8.3%
31–40	42.5%
41–50	39.9%
51–60	13.9%
>60	3.6%

Demographics – PMS individual

Gender (n = 162)	
Male	53.7%
Female	46.3%
Age group (years)	
0–3	14.0%
4–10	47.7%
11–17	22.2%
≥18	16.1%

Caregivers

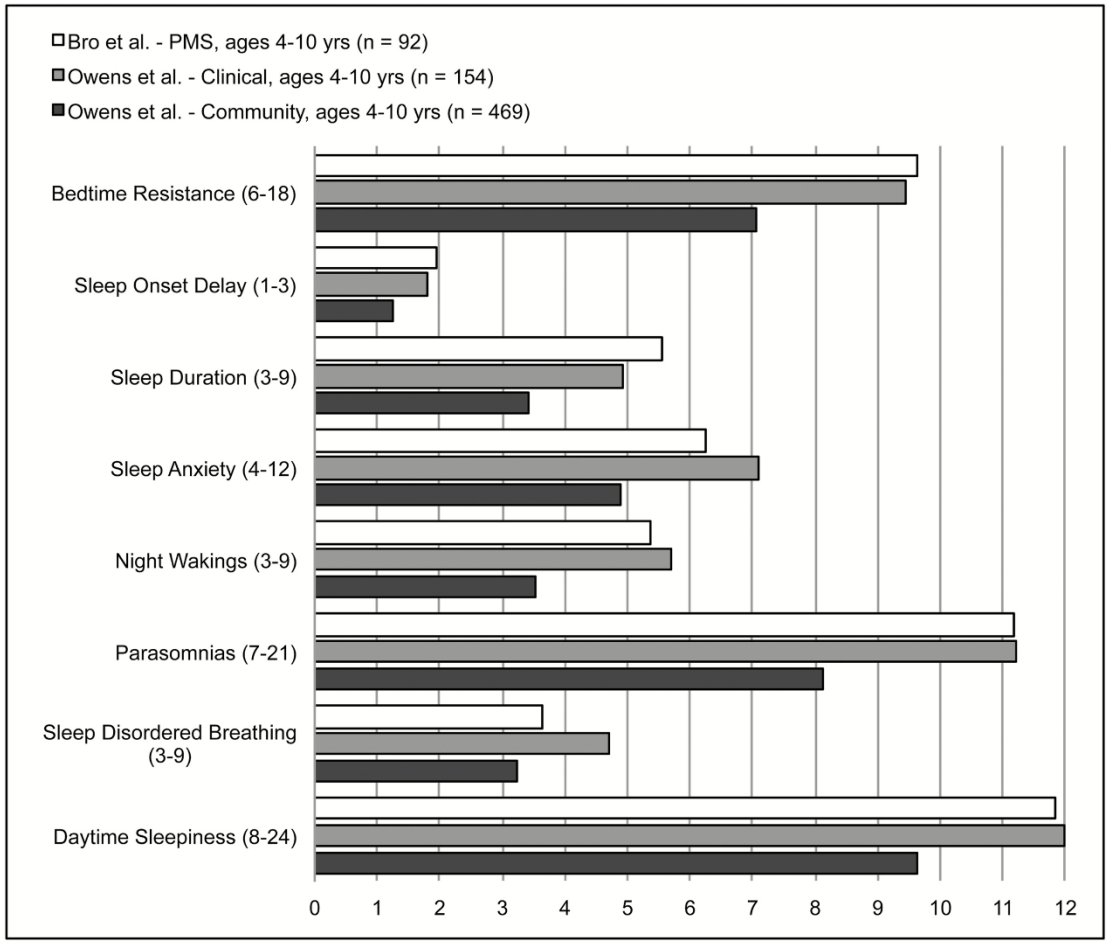
Primary overnight caregiver for child	
Myself	43.8%
Myself and my spouse/partner	51.6%
Other person (e.g. spouse/partner, hired caregiver)	3.6%

Employment and Hours of Caregiving – Caregivers

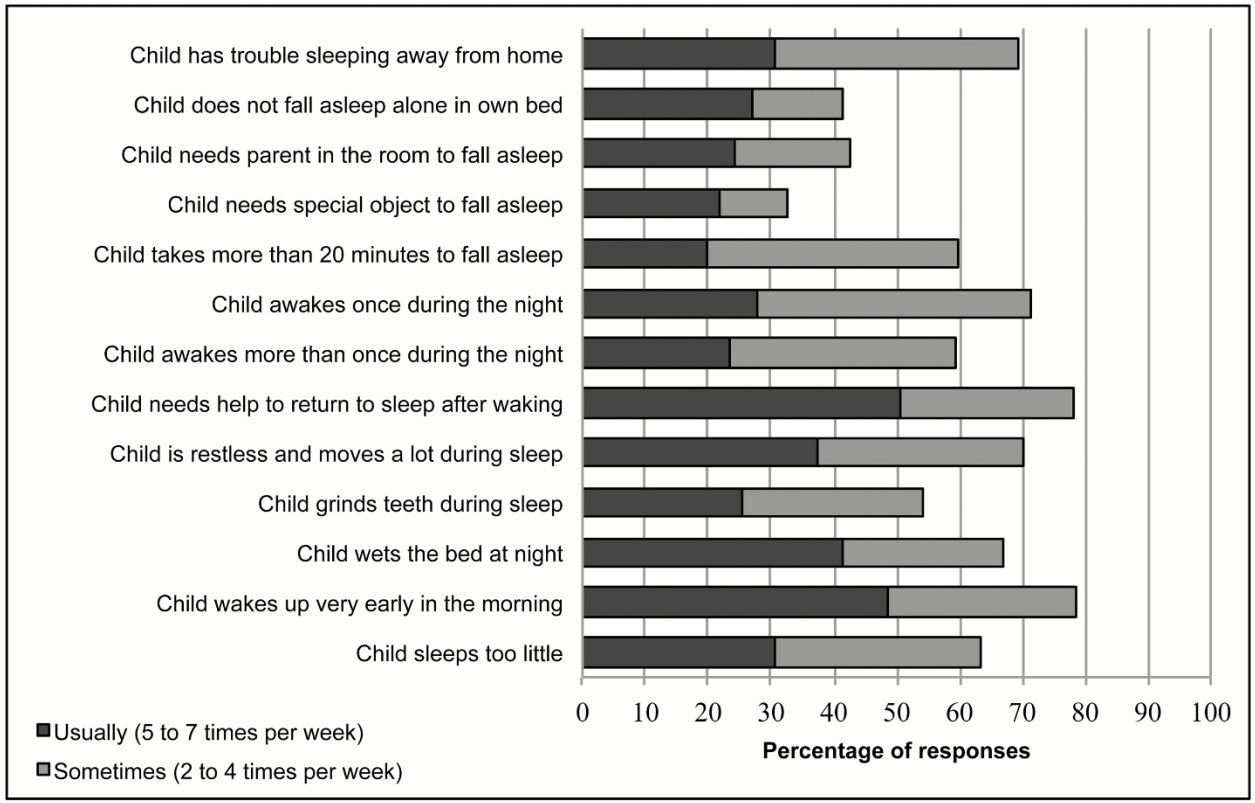
Employment status	
Not employed	32.8%
Part time	26.5%
Full time	40.7%
Hours of childcare assistance per week	
0–20	46.5%
21–40	38.0%
41–60	10.2%
>60	5.3%

Children's Sleep Habits Questionnaire

	<1–3 years	4–10 years	11–17 years	≥18 years	All ages
	(n = 25–27)	(n = 85–92)	(n = 40–43)	(n = 29–31)	(n = 179–191)
Subscales of CSHQ*	Mean score (SD)				
Bedtime resistance	**10.3 (3.5)**	**9.6 (3.2)**	**8.1 (2.8)**	**7.7 (2.4)**	**9.1 (3.2)**
Sleep onset delay	1.7 (0.8)	1.9 (0.8)	1.5 (0.6)	1.8 (0.7)	1.8 (0.8)
Sleep duration	**5.8 (1.8)**	**5.6 (2.0)**	**4.7 (1.7)**	**5.5 (1.9)**	**5.4 (1.9)**
Sleep anxiety	**6.8 (2.0)**	**6.2 (1.8)**	**5.9 (1.7)**	**5.8 (1.5)**	**6.2 (1.8)**
Night wakings	**5.8 (1.9)**	**5.4 (1.6)**	**4.9 (1.6)**	**5.2 (1.4)**	**5.3 (1.6)**
Parasomnias	**11.5 (2.1)**	**11.2 (2.8)**	**11.0 (2.1)**	**11.2 (2.0)**	**11.2 (2.4)**
Sleep disordered breathing	4.3 (1.8)	3.6 (1.1)	3.6 (1.0)	3.9 (1.2)	3.8 (1.2)
Daytime sleepiness	**12.2 (2.0)**	**11.8 (3.1)**	**11.6 (2.5)**	**12.6 (2.7)**	**12.0 (2.8)**
Total CSHQ score	**55.0 (9.8)**	**52.6 (9.3)**	**48.4 (7.5)**	**50.9 (8.0)**	**51.7 (9.0)**
% Above clinical cutoff score (≥41)	88.0%	88.2%	95.0%	89.7%	89.9%



Comparison of mean Child Sleep Habits Questionnaire (CSHQ) subscale scores among 3 samples: (1) children ages 4–10 years diagnosed with Phelan-McDermid Syndrome from the present study, (2) a clinical sample of children ages 4–10 years diagnosed with a sleep disorder from Owens et al.(2000), and (3) a community sample of children ages 4–10 years enrolled in public elementary schools from Owens et al. (2000) For all subscales, higher scores reflect more sleep disturbance. Minimum and maximum possible scores differed among subscales. The minimum and maximum possible scores for each subscale are shown in parentheses.



Caregiver responses to individual survey items from the Children's Sleep Habits Questionnaire (CSHQ). This figure includes all items for which 20% or more of caregivers reported that their child with Phelan-McDermid syndrome usually experienced a sleep behavior (*n* = 193).

Caregiver's Sleep and Daytime Function

- 82.4% felt that they did not get enough sleep
- Mean reported sleep time: 6.7 hours (SD=1.4)
- 40% reported less than 6 hours
- 43.8% awakened by their child 2-4 times per week
- 89.6% feel tired during the day
- 47.2% feel sometimes drowsy while driving

Predictors of Caregiver's Sleep

- Total sleep disturbance of individual with PMS ($p<0.001$)
- Female Gender ($P=0.009$)

Association of Caregiver's Sleep and Sleep of Individual with PMS

	Caregiver subscale scores		
Child subscale scores	Daytime sleepiness	Night waking	Sleep duration
Bedtime resistance	0.13	0.09	**0.25***
Sleep-onset delay	0.24	0.17	0.12
Sleep duration	**0.38***	**0.30***	**0.46***
Sleep anxiety	0.18	0.12	0.20
Night waking	0.19	**0.30***	**0.28***
Parasomnias	**0.32***	0.24	**0.27***
Sleep disordered breathing	0.19	0.21	0.13
Daytime sleepiness	0.27	**0.28***	0.11

***p* < .002**

Sleep Evaluations

- 22% of individuals with PMS have undergone formal sleep assessment

Diagnoses

- 62.5% (20/32) Sleep Apnea
- 18.8% (6/32) Insomnia
- 9.4% (3/32) Restless Leg Syndrome
- 6.3% (2/32) Periodic Limb Movement
- 3.1% (1/32) Narcolepsy

Sleep in Individuals with PMS

- Substantial proportion of individuals with PMS have marked sleep disturbance
  - Chronic
  - Limited proportion underwent formal sleep assessment
  - Of those diagnosed 60% had Sleep Apnea

- Long-term Impact on Caregivers
  - Caregiver Sleep routinely disrupted
  - Sleep Deprivation leads to complaints of Daytime Sleepiness

Conclusions -- Future Directions

- Substantial proportion of individuals with PMS have marked sleep disturbance
- **BUT** Sleep disturbance and/or Sleep Disorders are not regularly assessed in PMS
- Sleep disturbances in individuals with PMS are negatively associated with the self-reported sleep quality and daytime functioning of their caregivers
- Sleep disturbance can reflect a wide variety of sleep wake disorders and many can be treated -- When untreated may have a chronic negative impact on the well-being of both child and caregiver
- Future research utilizing objective sleep measures is required to more fully characterize sleep architecture, sleep disorders, and sleep disturbance in PMS

Future Directions in Sleep and PMS

- Few Parental Report Studies

- No Studies of Sleep in PMS Employing Standard Methodologies
  - Sleep Diaries
  - Actigraphy Measures of Activity
  - Video Recordings
  - Full Polysomnography (PSG): Gold Standard Assessment of Sleep

No PSG Assessment of Sleep Architecture in PMS

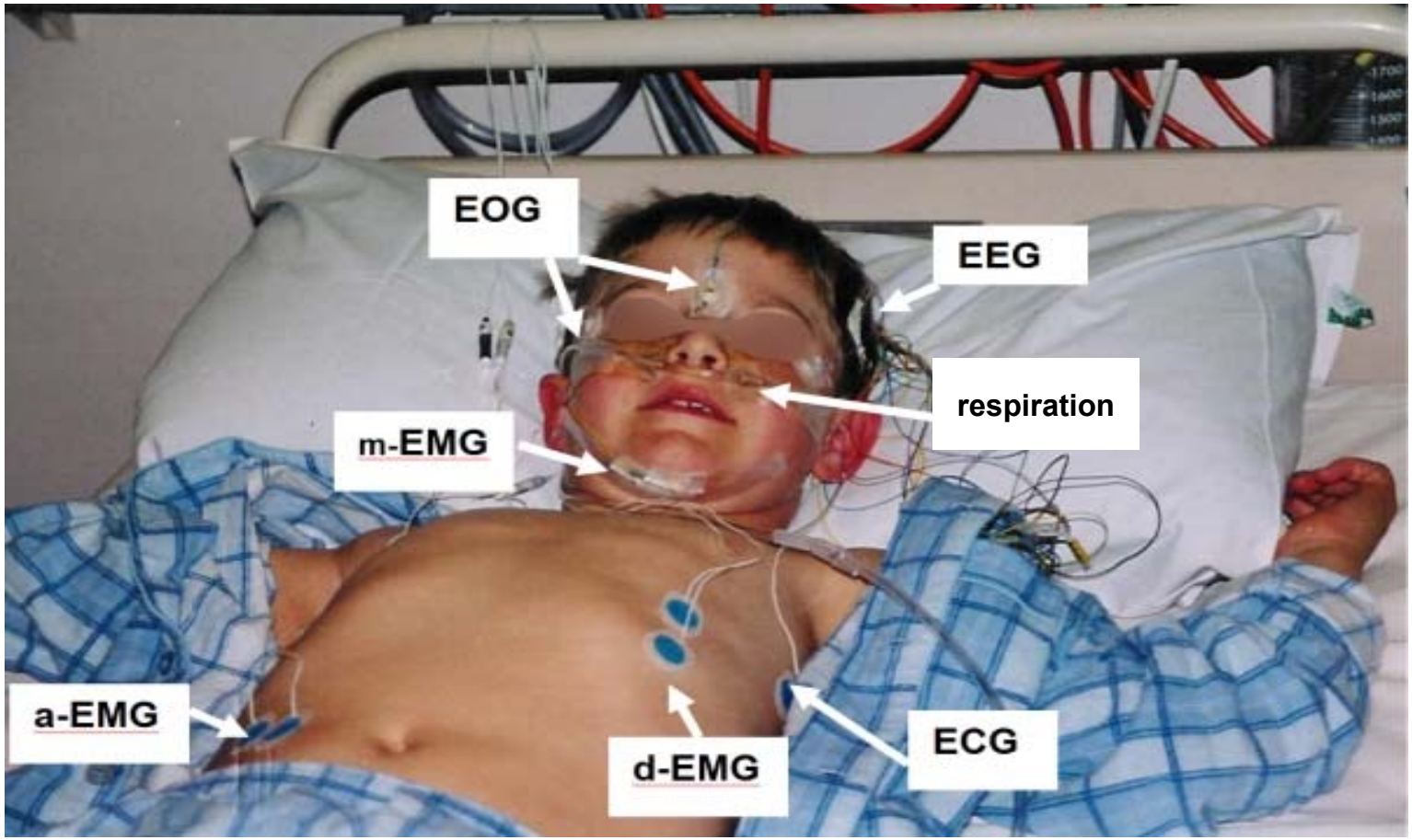
- Sleep Diaries, Actigraphy and Videos are valuable but limited as they Do Not Assess Sleep Architecture and do not capture Sleep Disorder Breathing or other Sleep Disorders

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

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

- Full Polysomnography is the Gold Standard to capture Sleep Architecture and Sleep Disorders

Is Full Polysomnography Assessment in PMS Possible?



Limitations of Overnight Laboratory Approaches

- Limited ecological validity
- Sample bias
- May be Difficult for Patients with PMS

O'Hara Lab: Pediatric Sleep Assessment with Ambulatory In-Home Polysomnography

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

Siesta Portable System

Recording Technical Specifications

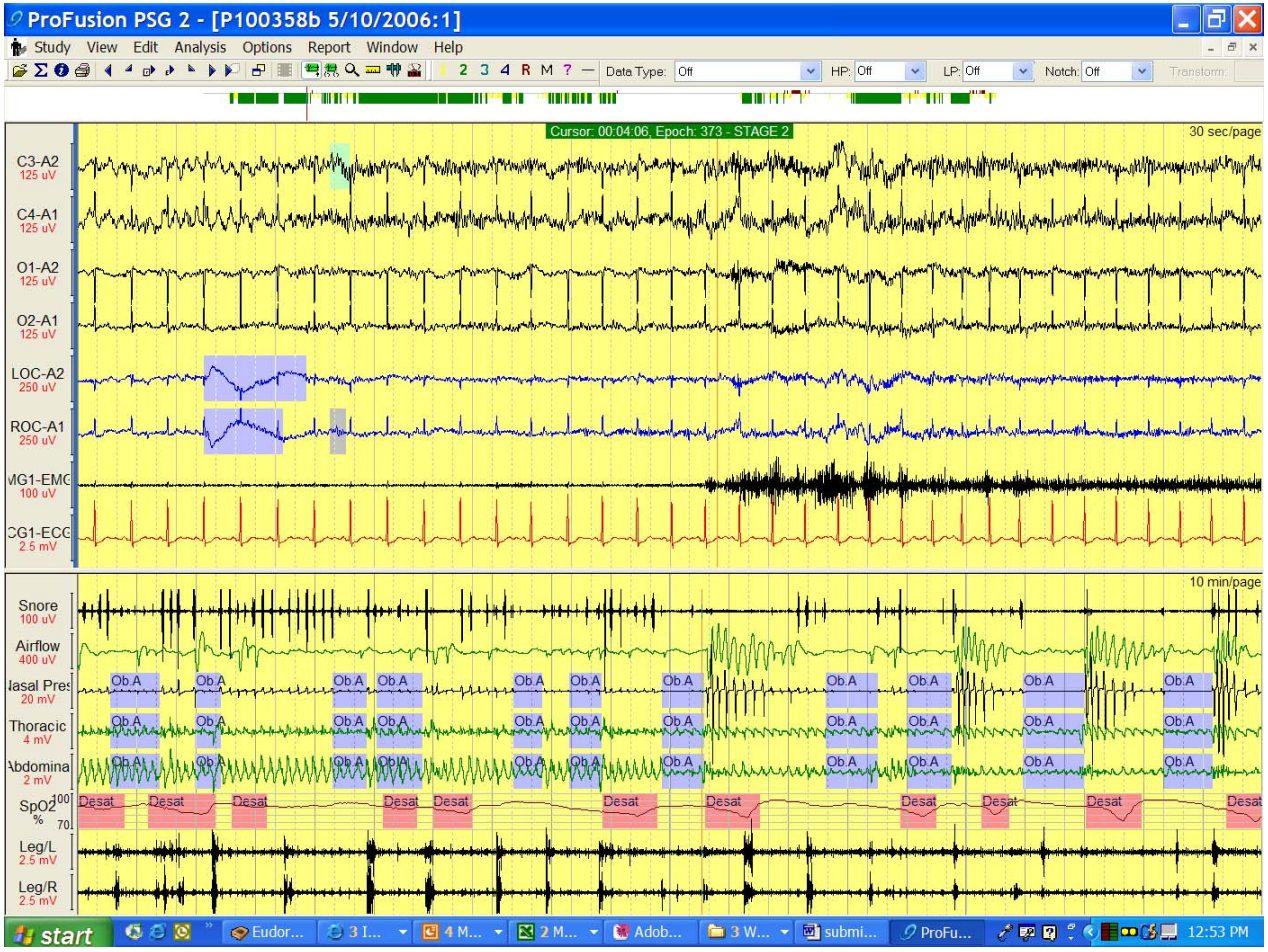
- 32 amplified universal channels for data collection
- Differential or Referential
- 16 bit resolution
- 512Hz sampling rate
- Two expansion ports for accessory modules: oximeter, pressure transducers, event button
- >48 hours data can be recorded using a Flash Card (1GB FAT file system)
- Operates on standard AA batteries

Data Monitoring

- Prior to lights-out, technician registers PSG and ensures quality data recording
  - Impedance
  - Quality signal of live data output
- Wireless connection between siesta and PC
- Technician may utilize Profusion 3 software to monitor data even during recording
- Patients free to move about during data monitoring

Pediatric Fully Ambulatory Polysomnography

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

Primeau et al.
(Journal of Clinical Sleep Medicine, 2015)

Study Objectives

Polysomnography (PSG) is the gold standard for the assessment of sleep, yet the extensive apparatus required for monitoring with PSG can be difficult to tolerate, particularly in children. Clinical populations, such as those with anxiety or tactile sensitivity, may have even greater difficulty tolerating the PSG equipment. This study evaluated an innovative protocol for obtaining full PSG in individuals diagnosed autism spectrum disorders (ASD) or developmental delay (DD), as well as typically developing controls (TD). The primary aim was to assess whether this protocol was equally successful for obtaining PSG between these groups.

Methods

One hundred sixty-one individuals were recruited for participation; 93 with a diagnosis of ASD, 23 with a diagnosis of DD, and 45 TD. The participants and families were instructed on a procedure of systematic desensitization to the ambulatory PSG equipment; PSG was performed in the home of the participant.

Results

PSG was successfully attained in 144 (89.4%) participants. There was no difference in completion rate by diagnosis ($p = 0.1$), though younger age ($p = 0.018$) and duration of desensitization ($p = 0.024$) did predict PSG failure. Further, it was found that individuals with ASD took longer to desensitize to the equipment (16.08 d), than those with DD (8.04 d) or TD (0.98 d).

Conclusions

Systematic desensitization to PSG equipment, in combination with PSG completed in the home, allows for individuals with ASD to be equally successful in completing PSG, though they do take longer to acclimate to the equipment.

Future Directions

- More Routine Clinical Assessment and Treatment of Sleep in PMS

- Increased Understanding of the nature of sleep disturbance in PMS via Objective Assessments including

  - Characterization of the Sleep Disorders in PMS
  - Determination of sleep architecture abnormalities in PMS
  - Understanding circadian rhythms and relationship to Sleep disturbance in PMS

- Future research utilizing objective sleep measures is required to more fully characterize sleep architecture, sleep disorders, and sleep disturbance in relationship to phenotypic presentation and longitudinal course in PMS

Thanks to All Families For Their Participation