Sleep Medicine 54 (2019) 101–112

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Prenatal alcohol exposure and sleep-wake behaviors: exploratory and naturalistic observations in the clinical setting and in an animal model

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ARTICLE INFO

Article history:
Received 6 August 2018
Accepted 13 October 2018
Available online 25 October 2018

Keywords:
Narrative
Video recording
Restless legs syndrome
ADHD
Mental health
Suggested clinical immobilization test

ABSTRACT

Introduction: Clinical research and studies using animal models have revealed a complex and relatively under-explored interaction between prenatal alcohol exposure (PAE) and alterations in sleep-wake behaviors.
Objectives: To utilize a structured naturalistic observation-based methodology, consisting of descriptive elements, to provide insight into possible links between altered sleep and disruptive daytime presentations in children and adolescents with fetal alcohol spectrum disorder (FASD). To apply a similar structured behavioral observation protocol in a PAE animal model to compare outcomes from the experimental and clinical studies utilizing naturalistic observational methodology.
Methods: Forty pediatric patients with FASD (1.8–17.5 yrs, median age 9.4 yrs) and chronic sleep problems were assessed. In the PAE animal model, male offspring from PAE, Pair-Fed (PF), and *ad libitum*-fed Control (C) groups (n = 8/group) were assessed in the juvenile/preadolescent (23–25 days of age) and adolescent/pubertal (35–36 days of age) periods.
Results: In the clinical setting, we found that 95% of children with FASD showed disruptive or externalizing behaviors, 73% showed internalizing behaviors, 93% had circadian rhythm sleep disorders, all had chronic insomnia, and 85% had restless sleep, often with tossing/turning/kicking movements indicative of non-restorative sleep with hypermotor events. In the daytime, individuals showed excessive daytime sleepiness as well as hyperactive/hyperkinetic behaviors, an urge-to-move, and involuntary movements suggestive of hyperarousability. Alterations in sleep/wake behaviors in the PAE animal model paralleled the clinical data in many aspects, demonstrating greater sleep latencies, less total time asleep, more total time awake and longer awake bouts, more position changes, more time in transition, and longer transition bouts in PAE compared to PF and/or control animals.
Conclusions: Thus, our findings provide support for the power and validity of naturalistic observational paradigms in revealing dysregulated sleep-wake behaviors and their association and/or exacerbating relationship with day and nighttime behavioral problems, such as disruptive behaviors, externalizing and internalizing disorders, and daytime sleepiness.

1. Introduction

Fetal alcohol spectrum disorder (FASD), which results from prenatal alcohol exposure (PAE), is the most common form of prenatally acquired brain injury [1–4]. and represents a major public and population health concern. Estimations of affected populations vary from 1% to 5% in North America and some Western European countries [5–8]. Children with FASD exhibit

Abbreviations: ADHD, attention deficit hyperactivity disorder; CRSD, circadian rhythm sleep disorder; C, control; FASD, fetal alcohol spectrum disorder; GD, gestation day; NDCs, neurodevelopmental conditions; PF, pair-fed; PND, postnatal day; PAE, prenatal alcohol exposure; RLS, restless legs syndrome.

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https://doi.org/10.1016/j.sleep.2018.10.006
1389-9457/

numerous alterations in day and nighttime functioning including neurocognitive deficits, impaired self-regulation and adaptive functioning, disruptive daytime behaviors, and sleep problems [9–15]. Sleep problems occur in up to 80% of individuals with FASD [16] and include short sleep duration, low sleep efficiency, decreased active sleep, increased sleep fragmentation, night awakenings, sleep disordered breathing, and parasomnias [17]. Disruptive daytime behaviors include externalizing and internalizing disorders, mainly attention deficit hyperactivity disorder (ADHD), oppositional defiant and obsessive-compulsive disorders, anxiety, depression, and sensory processing abnormalities [3,4,9,10], which can be exacerbated by [16] or even result from [13] dysregulated sleep.

Binge drinking during early pregnancy was shown to have strong predictive power for sleep problems during infancy [18], and alcohol-exposed infants showed increased sleep fragmentation [17]. Even pre-pregnancy alcohol consumption was found to correlate with maternal report of poor infant alertness [17]. Furthermore, lower birth weight and length were associated with lower sleep efficiency following prenatal alcohol and tobacco exposure [19]. These studies concluded that PAE disrupts postnatal sleep organization and that increased sleep fragmentation promotes sleep deprivation, which seems to be a chronic phenomenon that in turn could affect postnatal development. Disruptive daytime behaviors were also described, including difficult temperament [18] and increased irritability [17].

Although both clinical research [9–15], and animal studies [20–22], have highlighted these complex interactions between sleep and daytime behaviors, clinical practice has typically utilized daytime-related clinical explanatory models to explain the disruptive behaviors of children with FASD [23–25]. Unless asked specifically, even parental descriptions of their child's problems are focused almost solely on daytime behaviors [13,26]. Sleep, as a first line therapeutic target of disruptive daytime behaviors, has not been investigated in a systematic manner [13,16], resulting in a significant burden on the wellbeing of both the children and their caregiver families [9,13,27,28].

To capture the coexistence of disruptive sleep and wake behaviors in children and adolescents with neurodevelopmental conditions (NDCs) [13], we apply methods that allow for observation, exploration and description of naturalistic real-life situations [29]: emplotted narratives [13], structured daytime observations [30,31], and structured, video-based nighttime observations in the home setting [29,32–34]. In this context, emplotted is defined as working collaboratively with parents and caregivers (via exploration and negotiation of symptoms) to describe challenging/disruptive behaviors and then sharing the final summary for quality control. This approach facilitates self-description and observation of nighttime symptoms, which are otherwise not unveiled in time-constricted clinic visits, thus increasing our understanding of the interrelation between day and nighttime symptoms [31]. Notably, this methodology allowed us to capture the high prevalence of probable restless legs syndrome (RLS) in children with NDCs, including FASD [13,30,31]. RLS is a diagnosis based on the patient's verbal description of subjective symptoms, such as discomfort and urge to move in a resting state [33,35]. Among those who are able to express themselves, the prevalence of RLS is assumed to be approximately 2–3% [36], while in those who are unable to express themselves, RLS remains widely under-diagnosed [33]. Indeed, the restlessness associated with RLS is often confused with or misdiagnosed as ADHD [33,37]. Similarly, there is ambiguity in ADHD diagnoses in children with FASD [25,38]; despite the fact that ADHD is frequently diagnosed [39,40], the spectrum of ADHD presentations is not well-described [41], which may affect clinical treatment concepts [14,25].

Our naturalistic observation-based methodology allowed us to step-back from categorical diagnoses and capture the phenotypes of disruptive day- and nighttime behaviors characterized as: hyperkinesia, hypermotor events, and hyper/hypo-arousability ["H" behaviors]. Hyper-kinesia is a wake-state presentation of hyperactive behaviors that is used as a core diagnostic characteristic of ADHD [42], and goes along with hyper- and/or hypoarousability [43,44]. ADHD and/or anxiety present as hyperarousability while concentration difficulties and learning disabilities present as hypoarousability (delayed or uneven functioning). Traditionally, hypermotor restlessness, and hyper-/hypoarousability or arousal dysregulation [45] are terms established mainly in neurophysiology- (EEG-) based sleep (and wake) behavior research [46–49]. However, H-behaviors are also used as characteristic terminology in child psychiatry and mental health research (eg, to describe ADHD-, anxiety- or trauma-associated daytime behaviors) [50–52] or to describe an aroused state in different clinical contexts [53]. Reviewing the effects of PAE from the H-behavior perspective could reveal a novel explanatory model.

Studies using animal models of PAE support and extend the clinical literature demonstrating that PAE has significant short- and long-term adverse effects on the offspring, resulting in altered, "disruptive" daytime behaviors as well as alterations in the sleep-wake cycle and circadian rhythm. Impairments in self-regulation (eg, attention deficits, hyperactivity, deficits in response inhibition/habituation and regulation, hyperarousal, hyperresponsiveness to stressors, and increased depressive- and anxiety-like behaviors) and adaptive functioning (eg, attachment, feeding and suckling responses, and ultrasonic vocalizations [communication] in neonatal offspring, deficits in social behavior, and altered motor development) have been reported in animal studies [54–59]. Alterations in sleep behaviors include impaired sleep initiation, decreases in active sleep, increases in wakefulness, disruption of quiet sleep, reduced time spent in REM sleep, and increased latency to both slow-wave- and REM-sleep onset [60–63]. Reduced and fragmented slow-wave sleep along with reduced slow-wave bout duration and increased slow-wave/fast–wave transitions have also been observed in PAE compared to control animals [59]. Of relevance, a study on adolescent alcohol exposure found similar reductions in mean duration of slow-wave sleep episodes and total amount of time spent in slow-wave sleep in adulthood, suggesting that alcohol exposure across developmental periods has robust effects on slow-wave sleep [64]. PAE animals also show deficits in the ability to re-entrain physiological function and behavior to a new light–dark cycle following a circadian phase shift [65,66]. Of note, however, most of these studies have utilized short observation times and/or removed animals from their home cage and/or restrained or instrumented them during observation. While this allowed for a wealth of important behavioral and physiological data, the behaviors observed may not fully reflect what would be seen under more naturalistic undisturbed conditions.

To achieve our aim of capturing presentations of disruptive sleep-/wake-behaviors in real-life, natural settings, we applied a structured behavioral observation protocol (ie, naturalistic observations) in the clinical setting [31,34], and a similar behavioral observation protocol in our well-established PAE animal model in the home-cage environment [67]. This collaborative work investigates dysregulated sleep-wake behaviors and compares outcomes from the experimental and clinical studies utilizing the naturalistic observational methodology.

2. Methods

2.1. Clinical study

2.1.1. Patient population

This is a case series of patients with intractable chronic sleep problems, who had confirmed PAE with an FASD diagnosis and/or a prenatal alcohol history, assessed utilizing the Canadian diagnostic FASD criteria [3], which had caused child protection services to initiate intervention and/or assessment.

2.1.2. Sleep-wake behavior analysis in children and adolescents

We analyzed retrospectively data from assessments performed between 2011 and 2014 at the Sleep/Wake-Behavior Clinic (British Columbia Children's Hospital, the only quaternary care center in British Columbia), on 40 pediatric patients with major sleep problems who were referred by community-based practitioners after unsuccessful treatment attempts. The novelty of the structured assessment methodology as a clinical standard of care, utilizing the naturalistic listening, observing, exploring and describing methodology, with an assessor and trainee observer, has been explained in detail previously [13,14,29,31,68]. The clinical data were extracted from our database, which has been developed under UBC REB#: H15-00323 study (a retrospective chart study for patients seen at the Sleep-Wake Behavior Clinic between 2008 and 2015, based on the documentation of assessments). The interviewing techniques used during the clinical assessments were developed within UBC REB#: H09-00475 [13]; the refined assessment techniques were developed within UBC REB# H10-03466 [29]. Briefly, assessments included: (a) Clinical and narrative-based sleep-wake behavior history (emplotted narratives) [13,29,68], including a detailed medication history of past and current prescription/non-prescription medications; (b) An extended family sleep history (if birth parents and/or grandparents attended the assessment); (c) Structured behavioral observations using the formal and informal Suggested Clinical Immobilization Test (SCIT) (both direct quotations from patients and parents/caregivers and clinical observations were documented by a second observer throughout the assessment); (d) Sleep-wake behavior video recordings, if permitted by parents and/or legal guardian (see S1 Table for more information on the SCIT, video recordings, and definitions of observation-based descriptions analyzed in the clinical setting [31,34]); (e) Exploration of sensory processing, including auditory, tactile, visual, and oral domains [69]; and (f) A sleep-wake-behavior report, shared with the patient family as a quality control measure (for review/correction by the caregivers). The sleep-wake-behavior report included: (i) detailed description and summary of sleep-wake-behaviors (including excerpts of original quotations by patients/caregivers); (ii) our interpretations, which incorporated the caregivers' emplotted narratives in de-medicalized language; (iii) recommendations for caregivers and discussion of complex cases with involved community-based support teams. We used inclusive language at a grade five reading level comprehensible for any interested layperson.

2.2. PAE animal model

2.2.1. Breeding and experimental diets

Animals were bred in our central animal facility; detailed methods have been described previously [70]. Briefly, on day one of pregnancy, as confirmed by a vaginal smear, Sprague–Dawley female rats (n = 24) were assigned to one of three treatment groups (n = 8/group): (a) PAE dams were fed a liquid ethanol diet (Weinberg/Keiver High Protein Ethanol Diet #710324, 36% ethanol-derived calories), *ad libitum*; (b) Pair-fed (PF) dams were fed an isocaloric liquid control diet (Weinberg/Keiver High Protein Control Diet #710109), in the amount consumed by a PAE partner (g/kg body weight/day of gestation), with maltose-dextrin isocalorically substituted for ethanol. This controls for the reduced food intake that occurs with ethanol consumption; and (c) Control (C) dams were fed an isocaloric pelleted version of the liquid control diet *ad libitum* (Weinberg/Keiver High Protein Pelleted Control Diet #710109). Experimental diets, prepared by Dyets, Inc., Bethlehem, PA [71], were designed to meet nutritional requirements of pregnant animals, and were replaced with standard laboratory chow on gestation day (GD) 21. Parturition typically occurred on GD 22–23. All dams had *ad libitum* access to water throughout gestation and lactation.

At birth [postnatal day one (PND1)] litters were culled to 12 (six males, six females when possible). On PND 22, pups were weaned, paired-housed, and left undisturbed until testing. Only male offspring were tested in the present study due to logistical constraints; sex differences will be examined in future studies. Nevertheless, as most previous studies on sleep in PAE models were done on males, this allowed us to compare our results to other studies in the literature. All experimental protocols were in accordance with the NIH guidelines for the care and use of laboratory animals and the Canadian Council on Animal Care and approved by the UBC Animal Care Committee (UBC ACC# A14-0156).

2.2.2. Sleep-wake behavior analysis

Our analyses tested the hypothesis that sleep-wake behaviors would differ in PAE compared to PF and C offspring. Recordings occurred in the juvenile/pre-adolescent (PND 23–25) and adolescent/pubertal (PND 35–36) periods on pairs of rats (paired by prenatal group and in keeping with their social nature) in their home cages, which were transparent polycarbonate cages (24 × 16 × 46 cm), with pine-shaving bedding and wire grid tops. Animals were habituated to the facility for one day prior to the first day of recording. An infrared camera that provided an unrestricted "bird's-eye view" of each cage was used. Given the transparent cages and wire grid tops, a clear full view of each cage was possible. Videos recorded at each age were 26 h long (1840 h [lights off at 1900 h, lights on at 0700 h] on one day to 2040 h the next day) to capture lights-on and lights–off transitions, in accordance with the nocturnal cycle of the rat. The single recording session at each age was the basis for all analyses. Animals remained completely undisturbed while video recordings were in progress; cages were not changed on that day, and neither experimenters nor animal care technicians entered the experimental room for 6 h prior to and during the entire 26 h video session. Due to technical difficulties, videos were incomplete for one pair of animals at each age.

Cages were numbered so that prenatal group could not be identified, and videos were scored by two independent observers (KW, AH: kappa = 0.86), blind to the prenatal treatment of the animals. A standardized approach was used to analyze behaviors over the entire 12 h lights-on period and sleep-wake behaviors in the transition from lights off to lights on, measured from lights on until the animal fell asleep for a period of at least 5 min (the average length of a sleep bout as determined during video analysis). Sleep-wake behaviors included: Active behavior (playing, rearing, digging); Quiet behavior (grooming, eating/drinking, locomotion, standing or resting quietly), Twitches, and Sleep latency. For the 12-hr observations, behaviors included: Number of arousals, movements, and position changes; Total minutes awake, asleep and in transition; and Average length of awake, asleep and transition bouts (bout defined as minutes in one state prior to changing state). Criteria for assessing each behavior were standardized and the two individuals scoring the videos were trained extensively to these criteria and showed high inter-rater reliability (noted above). Videos

were viewed at 2x–8x speed to capture the behavioral patterns and then in real-time to further assess behaviors of interest; see S1 Table for definitions of behaviors scored in the animal model.

Two-way ANOVAs for the factors of group and age were performed using the Statistical Package for the Social Sciences software (SPSS, Inc, Chicago, IL). Newman–Keuls post-hoc comparisons were performed for all significant main or interaction effects; significant differences are indicated by * or # symbols in the text, figures, and figure legends. Further analyses included a priori comparisons (LSD) based on our hypothesis; significant differences are indicated by the "&" symbol. A p-value of <0.05 was considered significant, and p values < 0.10 were considered trends.

3. Results

3.1. Patients with FASD in the clinical setting

Out of 380 patients with NDCs seen at the Sleep/Wake-Behavior Clinic from 2011 to 2014, 49 (approximately 13%) patients met the inclusion criteria of FASD according to the Canadian FASD guidelines [3]. Twenty-nine patients had an FASD diagnosis with complete neurodevelopmental assessment of FASD-related morbidities; 11 patients had an FASD diagnosis based on confirmed PAE history with neurodevelopmental assessment under investigation. Nine cases were excluded due to incomplete information, leaving 40 patients for analysis (23 males, 17 females, mean age 9.1 years, median age 9.4 years, range 1.8–17.5 years). Table 1 presents an overview of the clinical description of the patient and day/nighttime presentations, which are summarized below.

3.1.1. Overall presentation at assessment

Amongst the 40 patients (see Table 1), 95% (38/40) were diagnosed with disorders of disruptive behaviors or externalizing disorders, with disruptive behaviors not otherwise specified (such as tantrums or aggression) being the most common presentation [70% (28/40)], and ADHD being the second most common [68% (27/40)]. Moreover, 73% (29/40) had an internalizing disorder diagnosis, with anxiety disorders [58% (23/40)] being the most common, followed by mood disorders (including depression) [43% (17/40)]. Typically, there was more than one presentation per patient; common neurodevelopmental presentations were global developmental delay/intellectual disability [25% (10/40)], uneven neurodevelopmental profile [45% (18/40)], and/or syndromes and/or other neurological disorders [60% (24/40)].

3.1.2. Sleep-wake behavior narratives

Daytime motor and behavior characteristics, indicative of H-behaviors, included descriptions such as 'always on the go', 'motor driven', 'fidgety' and were reported in 68% (27/40) of patients, consistent with the parental perception of fatigue or daytime sleepiness in 70% (28/40) of the patients; 45% (18/40) of patients had both excessive daytime sleepiness and hyperactivity, see Table 1. Nighttime motor and behavioral characteristics, indicative of H-behaviors, included 'visualizing' descriptions such as 'restless sleep, tossing and turning' and 'kicking movements' were noted in 85% of the patients (34/40), see Table 2. With the addition of confirmed and suspected periodic limb movements in sleep warranting investigation, this number increased to 95% (38/40), and were grouped as hypermotor events at nighttime, see Table 3. 93% (37/40) of patients fulfilled the criteria for circadian rhythm sleep disorder (CRSD): 98% (38/40) with delayed sleep onset subtype; 13% (5/40) with early awakenings; 25% (10/40) with a tendency for bi- or polyphasic sleep (note that three patients with typical napping habits below age six were excluded), see S2 Table for narrative-based visualizing descriptions.

3.1.3. Insomnia presentations (based on history and available logs/diaries)

All subjects experienced intractable chronic insomnia for longer than one year, 50% since early infancy: 98% (39/40) had problems

Table 1
Clinical description of patients: diagnoses & FASD-related morbidities.

	n	%
Prenatal Alcohol and/or Substance Exposure	**40**	**100%**
FASD (with completed neurodevelopmental assessment)	29	73%
FASD (neurodevelopmental assessment under investigation; PAE by history)	11	28%
Neurodevelopmental Morbidities	**34**	**85%**
Intellectual disability/Global developmental delay (ID/GDD)	10	25%
Autism spectrum disorders (ASD)	2	5%
Uneven developmental profile (only for patients without ID/GDD)	18	45%
Syndromes and neurological disorders[a]	24	60%
Mental Health Morbidities	**40**	**100%**
Externalizing disorders or disorders of disruptive challenging behavior	38	95%
ADHD/ADD	27	68%
Oppositional defiant disorder	8	20%
Disruptive/Challenging behavior NOS (ie, tantrums, aggression)	28	70%
Other externalizing disorders[b]	14	35%
Internalizing disorders	29	73%
Anxiety disorders	23	58%
Mood disorders (including depression)	17	43%
Post-traumatic stress disorder	5	13%
Excessive Daytime Behaviors	**37**	**93%**
Daytime sleepiness	28	70%
Daytime hyperactivity and/or disruptive behaviors	27	68%
Daytime sleepiness, hyperactivity and/or disruptive behaviors	18	45%
Chronic and Ongoing Sleep Problems	**40**	**100%**
Onset early infancy (described by parents as "since birth")	20	50%
Onset later in early childhood	5	13%
Onset not specified but longer than one year	15	38%

n = 40, mean 9.4 y/median 9.1 y; min 1.8 y; max 17.5 y; 23M/17F.

[a] Epilepsy, cerebral palsy, anatomical abnormalities, obesity, abnormal EEG/MRI, genetic abnormalities (CPT-1 deficiency), neurological disorders such heterotopia and other morbidities such as ataxia, tics and headaches.

[b] Obsessive-compulsive disorder, conduct disorder, neurobehavioral disorder, and attachment disorder.

Table 2
Presentations of most frequent sleep disorders in patients.

	n	%
Insomnia	**40**	**100%**
Difficulties falling asleep	39	98%
Despite medications	*26*	*65%*
Nighttime awakenings/sleep maintenance problems	37	93%
Despite medications	*4*	*10%*
Behavioral insomnia[b]	33	83%
Restless sleep with tossing/turning/kicking movements	34	85%
Despite medications	*4*	*10%*
Waking up early in the morning	6	15%
Restless Legs Syndrome (RLS)	**39**	**98%**
Confirmed/Suspected familial RLS	14/6	35/15%
Confirmed/Suspected RLS	12/7	30/18%
Parasomnias	**29**	**73%**
Sleep walking	8	20%
Sleep talking	12	30%
Teeth grinding	8	20%
Nightmares	18	45%
Night terrors	13	33%
Hypnagogic hallucinations	6	15%
Confusional arousals	6	15%
Sleep Disordered Breathing (SDB)	**38**	**95%**
Clinical Diagnosis of SDB	34	85%
Snoring	21	50%
Mouth breathing/dry mouth	32	80%
Drooling and/or motor hypotonia	6	15%
Witnessed apnea	3	8%
Bedwetting (age 5 and older)	11	28%
Sweating during sleep	16	40%
Uncomfortable/abnormal sleeping position to maintain open airways	6	15%
Difficulties getting up in the morning	19	48%
Circadian Rhythm Sleep Disorders	**37**	**93%**
With delayed sleep onset	36	90%
With early awakenings	6	15%
Bi- or polyphasic sleep[a]	10	25%
Anatomical/Craniofacial Characteristics leading to SDB	**27**	**68%**
Retrognathia	14	35%
Upper airway narrowing (eg adenoids)	17	43%
Ear infections/hearing loss	5	13%
Surgical interventions in the ENT region	6	15%

n = 40, mean 9.4 y/median 9.1 y; min 1.8 y; max 17.5 y; 23M/17F. Please note that that hyperkinesia, hyperarousability and hypermotor events have been investigated with day- and nighttime symptoms as possible organic causes of insomnia.
[a] Three patients who were aged six or younger were excluded due to their age.
[b] In all cases, behavioral insomnia was interpreted as secondary to an organize cause, eg, sensory processing abnormalities.

falling asleep and 93% (37/40) had sleep maintenance problems, see Table 2. Of note, 65% (26/40) of the group with problems falling asleep and 10% (4/40) with sleep maintenance problems showed symptoms of insomnia despite being medicated.

3.1.4. Non-restorative sleep

All patients presented with non-restorative sleep warranting further investigations: hypermotor events at nighttime occurred in 95% (38/40) of patients, see Table 3; similarly, 95% (38/40) of patients showed signs of sleep disordered breathing, 68% (27/40) showed signs of upper airway narrowing due to adenoids and/or anatomical facial features; and 73% (29/40) reported parasomnias, see Table 2.

3.1.5. Sleep-wake behavior video recordings

Eighteen home-based video-recordings were conducted [34]. All patients presented with motor and behavioral characteristics of 'restless sleep' and/or hypermotor events, confirming caregiver observations and behaviors that are part of our functional H-behavior concept: (a) fragmented and non-restorative sleep, such as spontaneous or several mini foot movements in series, including 'foot rubbing', which (b) usually ended in bigger limb movements, and resulted in (c) 'tossing/turning,' 'kicking,' and 'scratching' [72].

3.1.6. Formal sleep study reports

Four polysomnographic records were obtained: (a) one patient (age 12) had no pathological polysomnographic findings in regards to sleep architecture and signs of sleep disordered breathing; however, attention was drawn to the increased spontaneous arousals with an index of 9.2 per hour. All other patients had significantly affected sleep architecture with delayed sleep onset and/or sleep maintenance problems, explaining some potential causes of the clinical diagnosis of CRSD. (b) One patient (age 16) woke up after approximately 20 min and could not fall back asleep, confirming the clinical diagnoses of insomnia and CRSD. Within this short period, the patient showed snoring and had an apnea-hypopnea index of 7. Patients (c) (age 16) and (d) (age 17) had polysomnographies with affected sleep architectures. One had a normal REM latency and one had a prolonged REM latency, both had signs of significant sleep disordered breathing with increased apnea-hypopnea indices of 18 and 43, respectively, and, in both patients, periodic limbs movements were accompanied by respiratory events. These results confirm parental-reported observations of fragmented non-restorative sleep (described as restless sleep), are suggestive of hypermotor events, and are in accordance with hyperarousability (all had the diagnoses of anxiety and ADHD) and hypoarousability (all had the diagnoses of attention-deficit and

Table 3
Presentation of descriptive H-Behaviors in patients.

	n	%
Hypermotor Events at Nighttime	**38**	**95%**
Suspected periodic limb movements during sleep and/or probable high frequency of spontaneous arousals at nighttime[a]	29	73%
Abrupt leg/feet movements at daytime interpreted as increased frequency of spontaneous arousals at nighttime	14	35%
Sensory Processing Abnormalities as a probable trigger of H-Behaviors	**35**	**88%**
Sensitive to sensory input	24	60%
High pain tolerance	22	55%
Confirmed leg pain	8	20%
Suspected leg pain based on observational patterns	6	15%
H-Behaviors during Daytime assessed with SCIT	**37**	**93%**
Positive ***formal*** SCIT result (out of the **18** who were able to participate)	15	83%
Positive ***informal*** SCIT result[b] (out of **19** with an observation-based test)	17	90%
Inconclusive ***formal or informal*** SCIT result (out of **37**)[c]	3	8%
Negative ***formal or informal*** SCIT result (out of **37**)	2	5%

n = 40, mean 9.4 y/median 9.1 y; min 1.8 y; max 17.5 y; 23M/17F.
[a] Three confirmed by polysomnography and 18 confirmed by home-based video-recordings.
[b] Patients with a formal SCIT are excluded from this category.
[c] One patient was under medication, which may have affected his/her result.

major learning disabilities) at daytime. These sleep studies reveal that the in-depth dimension of the causes of H-behaviors are fully realized through laboratory-based testing.

3.1.7. Sensory processing abnormalities

Sensory processing abnormalities were present in 88% (35/40) of the patients, see Table 3. Of those, 60% (24/40) had heightened tactile sensitivity, 55% (22/40) had a high pain threshold, and 20% (8/40) had confirmed leg pain. Within the "high pain threshold" category, caregivers talked about their children responding in an unexpected/inappropriate manner to injuries (eg, "...broke his hand … but did not notice until later …; " "… fell …. on his face but did not cry …; " "...tripped and hit head, but laughed and walked away"). Within the "heightened tactile sensitivity" category, caregivers reported sensitivity to touch (eg, likes firm hugs/deep pressure, sensitivity to clothing tags, picks at themselves or "headbutts" peers, particular about food textures), see S2 Table for quotations from the clinical setting.

3.1.8. Suggested Clinical Immobilization Test

Ninety-three percent (37/40) of patients were assessed with a formal or informal SCIT, see Table 3; 49% (18/37) participated actively in the formal SCIT and 83% (15/18) of these reported some type of 'urge-to-move' and showed positive signs of involuntary movements of toes/feet/legs. For the 51% (19/37) of patients who could not participate in the formal SCIT due to insufficient comprehension (age or intellectual disability), observations of involuntary motor movements at random rest situations were utilized as an informal SCIT [31]. Three out of 37 patients had inconclusive results; two of these were on stimulant medications (methylphenidate and dextroamphetamine), which may have masked their presentation. Five percent (2/37) of the (formal or informal SCIT) tested patients did not have a positive result; these two presented as calm, with no abnormal limb movements or fidgeting during the assessment. However, one of these patients was on atomoxetine at the time, which was described to be making a "huge improvement" in his/her behaviors.

3.1.9. Medications

Eighty-three percent (33/40) of patients were on at least one medication (including melatonin, clonidine, trazodone, benzodiazepines, hypnotics or atypical antipsychotics prescribed for sleep) for challenges with insomnia. In addition, 60% (24/40) of patients were prescribed at least one psychoactive medication (including stimulants, atomoxetine, antidepressants, atypical antipsychotics, mood stabilizers, and α2-adrenergic agonists) for challenges with disruptive day- and nighttime behaviors. Moreover, 35% (14/40) of patients experienced an adverse drug reaction to prescribed psychoactive medications, and 28% (11/40) to medications prescribed for ADHD. Twenty-five percent (10/40) of patients were on at least one medication (including antihistamines, dimenhydrinate, diphenhydramine, fluticasone, albuterol sulfate, and salbutamol) for allergies and asthma; note that non-prescription antihistamines are also used as a remedy for insomnia. One patient was using a mometasone spray for sleep disordered breathing difficulties.

3.2. PAE animal model

3.2.1. Overall changes with age

ANOVAs for the factors of group and age revealed, as expected, significant main effects of age for a number of variables, indicating normal age-related changes in sleep-wake behaviors, independent of prenatal treatment (Table 4). Overall, at the start of the 12-hr lights-on (sleep) period, active behaviors ($F_{1,38} = 14.78$, $p < 0.001$) increased and quiet behaviors ($F_{1,38} = 14.80$, $p < 0.001$) decreased with age. In addition, the overall number of arousals ($F_{1,36} = 14.78$, $p < 0.001$) and movements ($F_{1,36} = 4.10$, $p < 0.05$) decreased, average duration of sleep bouts ($F_{1,36} = 14.41$, $p < 0.001$) increased, and average duration of awake bouts ($F_{1,36} = 8.26$, $p < 0.01$) decreased with age.

3.2.2. Disrupted sleep-wake behaviors

In addition to the overall changes in behaviors with age, we found that prenatal alcohol exposure differentially altered sleep-wake behaviors compared to those in PF and/or Control offspring. For sleep latency, the two-way ANOVA revealed main effects of age ($F_{1,38} = 11.80$, $p < 0.002$) and prenatal group ($F_{2,38} = 5.46$, $p < 0.01$). One-way ANOVAs by age followed by Newman–Keuls post-hoc comparisons indicated that at PND 23–25 ($F_{2,19} = 5.55$, $p < 0.02$), PAE showed longer sleep latencies than both PF and C ($^{*}p < 0.02$), while at PND 35–36 ($F_{2,19} = 3.56$, $p < 0.05$), PAE had longer sleep latencies than C ($^{*}p < 0.02$); PF showed intermediate latencies and were not different from either PAE or C (Fig. 1). In addition, while controls showed no changes in sleep latency from PND 23–25 to PND 35–36 ($p > 0.70$), PAE ($^{\#}p < 0.02$) and PF ($^{\#}p < 0.01$) animals both showed increased sleep latencies with age (Fig. 1). We further explored group differences over the 12 h observation period using LSD *a priori* comparisons, according to our hypothesis. We found trends for less total time asleep in PAE compared to C ($^{\&}p < 0.080$)

Table 4
Age-related changes in sleep-wake behaviors, independent of prenatal group.

Behavior	Pre-adolescent period (PND 23–25)	Adolescent period (PND 35–36)
Active behaviors	12.0 ± 3.0	30.1 ± 3.4****
Quiet behaviors	88.0 ± 3.0	69.9 ± 3.4****
Arousals	93.7 ± 3.3	75.7 ± 3.1****
Movements	612.4 ± 28.9	544.5 ± 18.5*
Duration sleep bouts (min)	4.2 ± 0.2	5.6 ± 0.3***
Duration awake bouts (min)	23.9 ± 1.4	18.9 ± 1.2**

Number or duration of behaviors (Mean ± SEM); * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0005$.

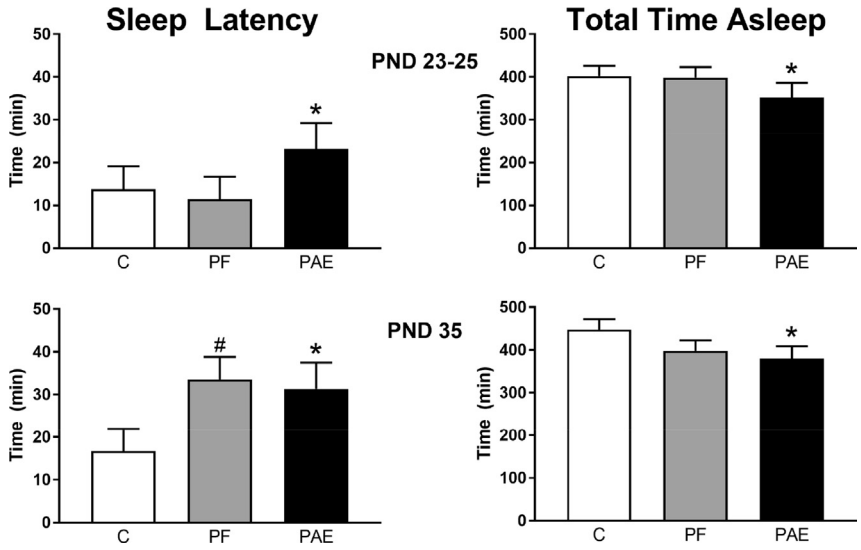

Fig. 1. Sleep latency and total time asleep. Left panels: At PND 23–25, PAE had longer sleep latencies than PF and C animals (*$p < 0.02$) while at PND 35–36, sleep latency was greater in PAE than C animals (*$p < 0.02$), with PF not different from either. In addition, both PAE (#$p < 0.02$) and PF (#$p < 0.01$) animals had increased sleep latencies with age, whereas C animals showed no change with age. Right panels: PAE showed a trend for less total time asleep compared to C animals at PND 35–36 (&$p < 0.080$). C, Control; PF, pair-fed; PAE, prenatal alcohol exposure.

at PND 35–36, Fig. 1) and more total time awake in PAE compared to PF (&$p < 0.05$) and C (&$p < 0.086$) at PND 23–25 (Fig. 2). Furthermore, while total time awake decreased to control levels in PAE animals by PND 35–36, mean duration of awake bouts was greater in PAE than C (&$p < 0.05$) at that time (Fig. 2). At PND 23–25, we also found more position changes in PAE (&$p < 0.02$) and PF (&$p < 0.05$) compared to C (Fig. 3). By contrast, at PND 35–36, total time in transition (&$p < 0.05$) and duration of transition bouts (&$p < 0.05$) were greater in PAE compared to C (Fig. 4). There were no effects of prenatal treatment or age on number of twitches.

4. Discussion

Our observational, exploratory and naturalistic methodology, applied to both clinical and animal studies, reveals consistent evidence that sleep-related problems are a fundamental part of the behavioral spectrum of FASD. These problems manifest interdependently as H-behaviors in both the wake and sleep states.

4.1. Observations in the clinical setting

All patients presented with FASD-related mental health morbidities and the associated disruptive behaviors appeared to cause major concerns, as 60% of patients were treated with psychoactive medications for their daytime presentations. The in-depth history revealed that the majority of children experienced intractable chronic insomnia since infancy or early childhood. This might explain why 85% of patients had been prescribed at least one medication for challenges with insomnia over the course of their lives. Given the broad range of over-the-counter medications (melatonin and antihistamine prescriptions are not regulated), this figure might be even higher. The home-based video recordings unveiled the dimension of thus far under-recognized “tossing … turning … kicking” movements during the night and confirmed the caregiver-reported narratives of alterations in sleep-related behaviors. For all of the behaviors scored, a majority (from 68% to 95%) of patients exhibited changes in both day- and nighttime behaviors. At night, patients had restless sleep with kicking movements (hypermotor events) causing insomnia. In the daytime, they presented with externalizing behaviors, excessive daytime sleepiness, ADHD with hyper- and hypo-arousability, and internalizing disorders. There was an overlap of hypermotor and hyperkinetic events with excessive daytime sleepiness in 45% of patients. A majority also had sensory processing abnormalities, in which H-behaviors were again a major observable component that affected the perception of stimuli and increased pain threshold.

Overall, these results confirm the co-occurrence of disruptive daytime behaviors with chronic sleep problems, mainly intractable insomnia, and support the concept of H-behaviors as the common denominator of both day and nighttime behaviors in patients with FASD. These data support and extend previous studies that investigated the link between sleep problems and disruptive daytime behaviors in infants [17–19], schoolchildren, and adolescents [15], with an FASD diagnosis. Similarly, a previous study found that sensory processing abnormalities can aggravate not only intractable chronic insomnia but also disruptive behaviors [12].

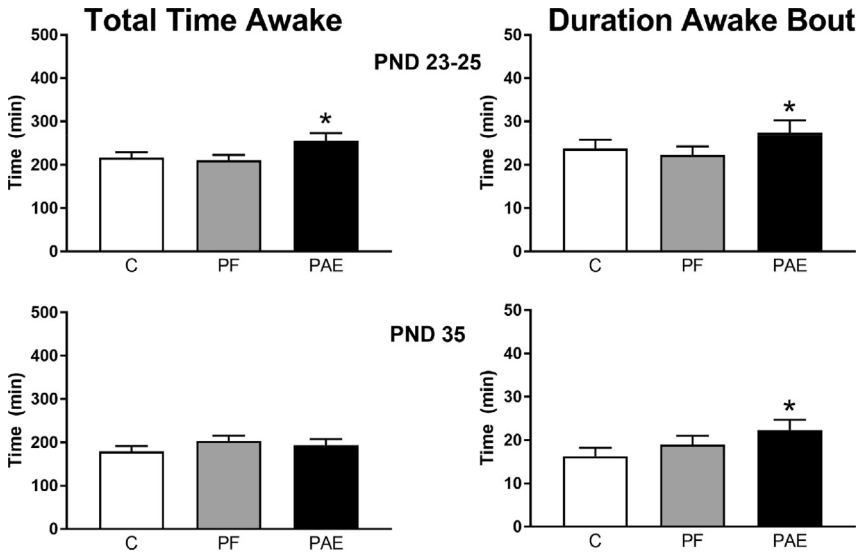

Fig. 2. Total time awake and mean duration of awake bouts. PAE spent more total time awake than PF ($^{\&}p < 0.05$) and showed a trend for more time awake compared to C ($^{\&}p < 0.086$) animals at PND 23–25. PAE also showed a longer mean duration of awake bouts compared to C animals ($^{\&}p < 0.05$) at PND 35–36. C, Control; PF, pair-fed; PAE, prenatal alcohol exposure.

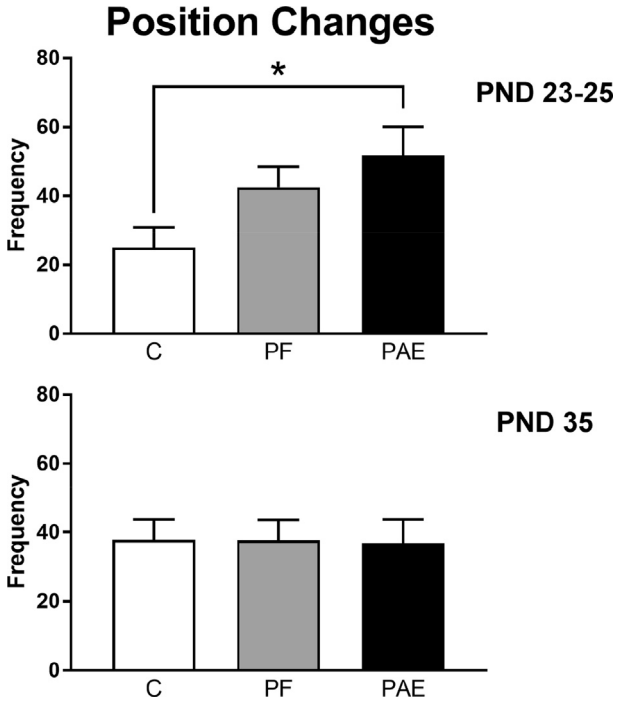

Fig. 3. Total position changes. Total number of position changes was greater in PAE ($^{\&}p < 0.02$) and PF ($^{\&}p < 0.05$) compared to C animals at PND 23–25. C, Control; PAE, PF, pair-fed; PAE, prenatal alcohol exposure.

4.2. Observations in the animal model

The findings in our animal model reveal sleep-wake disturbances consistent with those found in the clinical setting. In parallel with the early onset of sleep problems in infants with FASD [18], and their persistence over time [16], PAE animals showed longer sleep latencies, spent less time asleep and more time awake, and had longer awake bouts than their PF and/or control counterparts. As well, we observed increased numbers of position changes, more time in transition and longer transition bouts in PAE compared to control animals, which parallel the clinical findings of more restless or non-restorative sleep. Together with previous studies in the literature, our findings suggest a possible correlate to the insomnia and H-behaviors seen in children with FASD.

These data are complementary to and build on previous studies in animal models that utilized short observations and/or removed animals from their home cages, and restrained and/or instrumented them during observations for the collection of physiological data [60–63,65,66]. The observational approach of the present study places sleep in a more complete context by considering both sleep and wake behaviors. However, this strength might also be considered a possible limitation of our methodology, as assessment of behavior was by observation only, albeit using standard set criteria for each behavior scored. One cannot confirm that the animal is asleep, and certainly cannot assess stages of sleep, without the use of electrophysiological recordings, as demonstrated in previous studies [59–64]. Nevertheless, our study fills a gap in the literature; it is the first to utilize prolonged observations over a 24+ hr period, across light-on/lights–off transitions, to assess sleep-wake behaviors under naturalistic home cage conditions. While instrumenting an animal provides accurate and important neurobiological and physiological data, these procedures in themselves could alter sleep-wake states and behaviors, and may not fully reflect the behaviors that occur under undisturbed conditions. The fact that the behaviors observed in our animal model not only broadly replicate some of the previous findings in the literature but also parallel the clinical findings, supports the power and importance of this observational methodology.

The instances where we saw similar behaviors in pair-fed and PAE animals likely do not reflect the same underlying mechanism(s). While pair-feeding is the accepted standard procedure to account for the reduced intake typical of alcohol-consuming animals, it is at best an imperfect control and in many ways, a treatment in itself [73]. Although both PAE and PF treatments result in reduced food intake by the dam and thus mild undernutrition of the fetus, pair-feeding can never control for alcohol's nutritional effects, including its impact on absorption and utilization of nutrients. Moreover, while alcohol-consuming females consume their food *ad libitum* over the 24 h period, the reduced ration presented to pair-fed females results in consumption of their entire daily

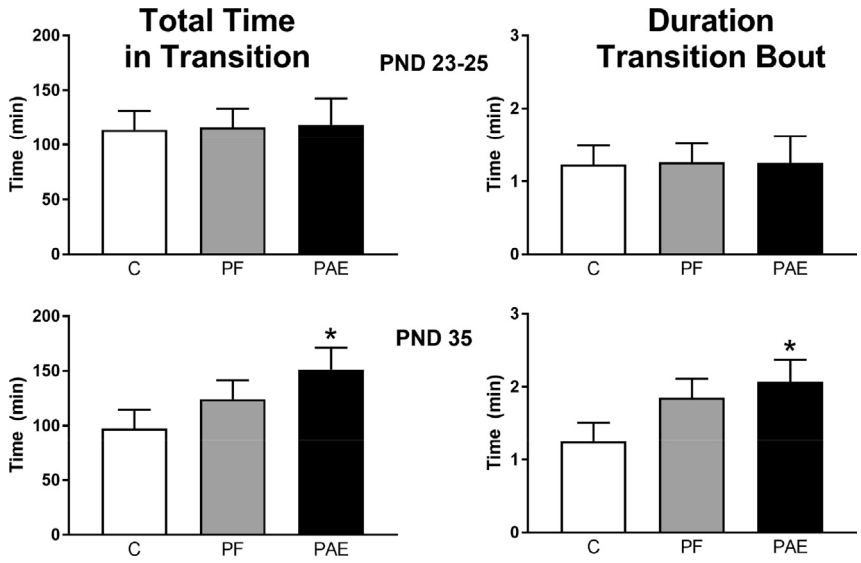

Fig. 4. Total time in transition and mean duration of transition bouts. Both total time in transition ($^{\&}p < 0.05$) and mean duration of transition bouts ($^{\&}p = 0.05$) were greater in PAE compared to C animals at PND 35–36. C, Control; PF, pair-fed; PAE, prenatal alcohol exposure.

ration within a few hours. These females are then hungry for the remainder of the 24-h cycle and therefore are more behaviorally aroused and experience some level of mild stress compared to their alcohol-consuming counterparts. The pair-feeding regimen (effectively, a "meal-feeding" schedule) is also known to have a number of metabolic effects [74–76], and to cause a phase shift in circadian periodicities of protein synthesis, certain liver enzymes, brain tryptophan, body temperature, running activity and HPA activity [77–79], which in themselves could alter behavioral and physiological function of offspring [80,81].

4.3. Significance and impact of our results

The interdependence of sleep and wake problems in children and adolescents with FASD has been under-recognized in clinical practice and therefore has often not been considered in the development of therapeutic strategies thus far. Factors that may account for this lack of recognition include: (a) the overshadowing of the effects of sleep disturbances by disruptive daytime behavioral alterations and the fact that behavioral problems that occur at night may be thought of as characteristics of FASD rather than as sleep problems [26]; (b) the belief that sleep has to be investigated in a lab environment, as sleep studies are the "gold-standard" [13]; and (c) the predominantly missing phenomenology of disruptive H-behaviors, which divides parental and professional perceptions and connotation of symptoms [29]. The results of our approach show that: (a) that sleep should always be included in the diagnostic evaluation of every child with FASD who presents with a spectrum of disruptive daytime behaviors, even in the absence of caregiver or self-report of a concomitant sleep problem; and (b) the importance of caregivers' narratives, emphasizing the role of descriptive visualizing observations in the clinical history.

The current understanding is that disruptive daytime behaviors may affect sleep initiation, and result in circadian rhythm disorders and possibly melatonin deficiency or delayed melatonin onset [16], which have been observed in children with NDCs [93–96]. Consequently, physicians typically target daytime behaviors first, which can result in a cascade of prescriptions for psychotropic medications, and has led to overmedication and even polypharmacy, further complicating clinical presentations [14]. Indeed, children with PAE are diagnosed with ADHD more frequently than those without an FASD diagnosis [9,13,27]. ADHD-like H-behavior symptoms are a frequent target for pharmacological interventions with psychostimulants despite indications that the complexity of behavioral problems in FASD cannot be explained by an ADHD-related pathophysiology alone [41,97], and the high frequency of variable and/or adverse responses to medications in this population [14,23,24,38,98–102]. In our clinical sample, 60% of patients were on psychotropic medications and almost 45% had shown adverse drug reactions, necessitating the prescription of other medications. Consistent with these findings, a recent study utilizing our animal model found that PAE rats exhibit a lower threshold for amphetamine sensitization than controls, suggesting a possible basis for the frequent adverse responses to stimulant medications in children with FASD [103].

The complexity of symptoms and problems in children with FASD, coupled with the lack of recognition of the interdependence of sleep and wake problems that often occurs, shifts the focus to diagnosis rather than the phenomenology of observations. Currently, FASD guidelines reflect this clinical diagnostic framework as sleep disorders are still not included as part of the functional differential diagnosis of ADHD-like behaviors [3,4], despite publications questioning ADHD per se as the cause of disruptive daytime behaviors in children with FASD [27,41]. Therefore, we suggest: (a) encouraging descriptive narratives and capturing them through in-depth history-taking, including the use of video clips of disruptive behaviors; (b) implementing structured observations in the assessment of disruptive H-behaviors, eg, with the SCIT, in order to include caregiver observations in a more in-depth manner than previously done; (c) developing a shared language through the discussion and negotiation of symptoms, which will (d) facilitate phenotyping to overcome the current categorical diagnostic model.

The pathophysiology underlying dysregulated sleep-wake and H-behaviors remains to be elucidated. Promising avenues of research supported by data from both PAE animal models and clinical studies include: (a) The adverse effects of altered iron status on key characteristics of FASD [20–22,82,83]. The finding that iron deficiency also plays a pathogenic role in conditions associated with H-behaviors, such as RLS [33,35], ADHD [84,85], and tics [86],

is further evidence for its importance. Moreover, patients from our clinic with other NDCs (eg, autism) and iron deficiency presented with intractable chronic insomnia, similar to the patients described herein [30]. (b) The role of hypothalamic-pituitary-adrenal (HPA) dysregulation in sleep disturbances, including insomnia. Several studies have demonstrated altered HPA activity and regulation in FASD and this can support the possible role of cortisol in sleep-wake disturbances [87–92]. Investigation of these and other possible mechanisms is a key target for future research.

5. Conclusion

Our exploratory and naturalistic observational approach allowed us to obtain insight into the sleep-wake behaviors of children in the clinical setting and to replicate our approach, methods and findings in a well-established animal model. In the clinical-setting, history-taking and exploration of caregiver narratives improved standard clinical practice and allowed us to develop a shared language among parents, professionals, and researchers [13]. Significantly, the observational methodology applied in our experimental animal study revealed the persistent dimensions of disrupted sleep and wake behaviors that are possible correlates of insomnia and H-behaviors observed in children with FASD. These findings not only justify further research but also the re-launching of a traditional but foundational concept, namely, listening, observing, exploring and describing in clinical assessments of disruptive day- and nighttime as well as sleep behaviors. The parallel nature of the observations between the settings will allow us to explore basic physiological and neurobehavioral mechanisms in the animal model and to move from the clinic to the laboratory and back again and thus more rapidly advance our clinical practice. Application of this concept will facilitate a shift from categorical diagnoses to a phenomenological, semiology-oriented understanding of disruptive behaviors that captures the critical role of sleep in the context of behavioral problems in children with FASD.

Acknowledgments

In Dr. Ipsiroglu's laboratory, the clinical research was funded by The Fetal Alcohol Spectrum Disorder (FASD) Action Fund through the Victoria Foundation [grant number 07–2444], BC Children's Hospital and the BC Children's Hospital Research Institute (formerly Child and Family Research Institute) via the Treatable Intellectual Disability Endeavour [grant number F11-00419], and the Kids Brain Health Network (formerly NeuroDevNet), Canadian Networks of Centres of Excellence [grant number 20R72932].

In Dr. Weinberg's laboratory, the animal model research is funded by NIH/National Institute on Alcohol Abuse and Alcoholism [grants number R37 AA007789 and number RO1 AA022460], and Kids Brain Health Network (formerly NeuroDevNet) (Canadian Networks of Centres of Excellence [grant number 20R23427]).

We would like to extend our gratitude to Mr. Gerhard Kloesch for his critical review and constructive discussion in the presentation of the results, and to Parker J. Holman for the statistical analyses and the figures.

Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, or publication of this article.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.10.006.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2018.10.006.

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