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A Review of Sleep Disturbances among Infants and Children with Neurodevelopmental Disorders

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Abstract

Sleep problems are common among children with neurodevelopmental disorders (NDDs). We review sleep disturbance in three major NDDs: autism spectrum disorder, Down syndrome, and fetal alcohol spectrum disorder (FASD). We review associations with functional impairment, discuss how patterns of sleep disturbance inform understanding of etiology, and theorize about mechanisms of impairment. Sleep disturbance is a transdiagnostic feature of NDDs. Caregivers report high rates of sleep problems, including difficulty falling or staying asleep. Polysomnography data reveal differences in sleep architecture and increased rates of sleep disorders. Sleep disturbance is associated with functional impairment and stress among families. Further research is needed to elucidate mechanisms of impairment and develop more effective interventions. Despite significant sleep disturbance in FASD, limited research is available.

Keywords

sleep; sleep problems; developmental disorders; autism; Down syndrome; fetal alcohol

Sleep disturbance has emerged as a transdiagnostic feature of numerous mental health conditions across the lifespan (e.g., Harvey, Murray, Chandler, & Soehner, 2011; Meltzer et al., 2017). Such findings extend to neurodevelopmental disorders (NDDs), including autism spectrum disorder (ASD), Down syndrome (DS), and fetal alcohol spectrum disorder (FASD). For those with NDDs, severity of sleep disturbance often correlates with medical problems and functional impairment (e.g., Hollway, Aman, & Butter, 2013). Thus, specifying sources of sleep disturbance may improve our understanding of etiology, which is often a precondition for developing effective treatments (Beauchaine, Neuhaus, Brenner, & Gatzke-Kopp, 2008). Furthermore, high rates of sleep disturbance, associations with

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increased impairment, and evidence of effective interventions make it increasingly clear that healthcare providers who work with children with NDDs need to identify and target sleep problems as standard practice (Lord, 2019). In this article, we (1) summarize the burgeoning literature on sleep problems among children with ASD, DS, and FASD; (2) review sleep architecture for each disorder; (3) describe associations with functional impairment; (4) explore possible mechanisms of impairment; and (5) identify gaps in the research literature that should be addressed in coming years.

1. Sleep primer

For purposes of this review, *sleep problems* refer to reports of sleep concerns, whereas *sleep disturbance* refers to combinations of sleep problems, sleep disorders, and disrupted sleep architecture. Sleep problems can be classified broadly into sleeplessness, excessive daytime sleepiness, and parasomnias (Wiggs & Stores, 2004). Sleep problems are usually conceptualized along severity continua, whereas sleep disorders are often construed categorically. Sleep problems often overlap with sleep disorders (e.g., sleeplessness and insomnia). Estimates of sleep problems among typically developing children range from 25–40% (Meltzer & Mindell, 2006; Owens, 2007).

Sleep is often divided broadly into two phases, including non-rapid eye movement (NREM, ‘quiet’ sleep), and rapid eye movement (REM, ‘active’ sleep). REM refers to twitching of eye muscles that occurs in this phase of sleep (Finn Davis, Parker, & Montgomery, 2004). These broad phases are further subdivided into different stages. During NREM, Stage 1 (N1) consists of light sleep from which people easily awaken. In Stage 2 (N2) sleep, EEG patterns of sleep spindles and K-complexes appear (Fogel & Smith, 2011). Sleep spindles are oscillating bursts of EEG activity that reflect thalamocortical processing. K-complexes are N2 waveforms that may reflect both bottom-up subcortical information processing and top-down cortical suppression to preserve sleep (Jahnke et al., 2012). Stage 3 (N3)—sometimes referred to as deep sleep or slow wave sleep (SWS)—is characterized by delta waves (0.05–4.0 Hz oscillations; see Krystal & Edinger, 2008). During REM, cortical activity increases, and large muscle groups exhibit paralysis. Vivid dreams occur that are often remembered. REM is hypothesized to play an important role in formation of neural connections, which proliferate in early childhood (Marks, Shaffery, Oksenberg, Speciale, & Roffwarg, 1995).

S*leep architecture* refers to the structure of sleep stages, which change over childhood (Mindell & Owens, 2015). For example, healthy infants spend about 50% of sleep time in REM, compared with 25–30% for adolescents and adults (McCarley, 2007). SWS and REM sleep deprivation produce rebound (more sleep) in recovery nights, which suggests they serve homeostatic functions (e.g., Verma, Radtke, VanLandingham, King, & Husain, 2001).

2. Sleep measures

Prior to describing patterns of sleep disturbance in NDDs, we briefly summarize sleep assessment methods commonly featured in the literature. For further information and a comparison of methods, please see Sadeh, 2015.

2.1 Polysomnography

Polysomnography (PSG) is a standardized method for measuring sleep, and is necessary for diagnosis of certain disorders, such as sleep apnea (Kothare & Kaleyias, 2008). PSG uses electroencephalogram (EEG), electrooculogram (EOG), and a chin electromyogram (EMG) to measure brain activity and body movements during sleep. Chest, abdominal belts, and nasal thermistors measure respiration and respiratory effort. Two nights of PSG are recommended as the first night may reflect adjustment to the environment (NIMH, 2016). Although PSG is considered the gold standard for sleep evaluation, it is time-consuming and expensive. Therefore, it can be difficult to conduct with large samples. Furthermore, it can be difficult to use with children, particularly those with NDDs, as they may not tolerate the equipment or sleeping away from home. Variables of interest include total sleep time (TST), sleep onset latency (SOL), wake after sleep onset (WASO), and sleep efficiency (percentage of time spent asleep; SE) (Krystal & Edinger, 2008). PSG also provides information about periodic leg movements and sleep architecture, including sleep spindles.

Sleep spindles are a measure recommended by the National Institutes of Mental Health (NIMH) in their Research Domain Criteria (RDoC) for arousal and regulatory systems (NIMH, 2016). As described earlier, sleep spindles are distinctive bursts of EEG activity that occur throughout NREM sleep, but feature predominantly in N2 (De Gennaro & Ferrera, 2003; Fogel & Smith, 2011). They are generated in the thalamic reticular nucleus and reflect electrical activity resulting from thalamocortical loops. Sleep spindles generally oscillate between 12–16 hz across the sigma frequency band. Number and/or density of sleep spindles are often described (NIMH, 2016). Within individuals, the number of sleep spindles tends to remain stable from night to night (Fogel, Nader, Cote, & Smith, 2007). Sleep spindles correlate with learning and memory consolidation (Clemens, Fabó, & Halász, 2005; Fogel & Smith, 2006). Transcranial stimulation and medications can increase sleep spindles experimentally. Studies that use these techniques demonstrate corresponding increases in memory consolidation (Mednick et al., 2013; Lustenberger et al., 2016).

Additional sleep parameters measured with PSG include EEG frequency spectral analysis during NREM sleep, which analyzes amount of EEG activity across various frequency bands (e.g. delta [0.5–4 Hz], theta [4–8Hz], alpha [8.5–12 Hz], etc.) (Krystal & Edinger, 2008). Delta power, in particular, is thought to represent the homeostatic sleep drive (process S). Measuring average delta power and the rate of decline in delta power may provide further information about this process (NIMH, 2016). The cyclic alternating pattern (CAP) is an EEG marker of sleep instability during NREM sleep (Krystal & Edinger, 2008; Parrino, Ferri, Bruni, & Terzano, 2012). CAP is a promising objective measure of sleep quality. For example, CAP rates are negatively correlated with subjective ratings of sleep quality.

2.2 Actigraphy

Actigraphy is less invasive and costly than PSG and is used widely in sleep research (Kothare & Kaleyias, 2008; Krystal & Edinger, 2008). Actigraphs are small, computerized devices that children wear on their non-dominant wrist or ankle. They provide a general estimate of sleep-wake cycles by measuring activity levels. In order to get a representative sample of data, children should wear the actigraphs for at least 1–2 weeks. Sleep diaries are

also recommended to assist with data interpretation. Sleep parameters are similar to those collected with PSG and include SOL, TST, WASO, and SE. A review of the literature suggests that actigraphs have higher sensitivity than specificity when compared with PSG (Meltzer, Montgomery-Downs, Insana, & Walsh, 2012). Actigraphs are unable to differentiate between sleep and quietly lying still and, therefore, may overestimate sleep time. However, findings from a number of studies also suggest that actigraphy may underestimate total sleep time. Therefore, actigraphy may be better suited as a general measure of circadian rhythms, as opposed to a precise measure of sleep (NIMH, 2016).

2.3 Caregiver/self-report

Caregiver or self-report measures are a popular method in sleep research, due to their ease of administration. Sleep diaries provide a rough estimate of a child's sleep-wake patterns and can be used independently or as an adjunct to actigraphy. Some studies collect data with validated questionnaires. The Children's Sleep Habits Questionnaire (CSHQ) is one of the most widely used questionnaires to assess sleep problems in children (Owens, Spirito, & McGuinn, 2000). This parent-report questionnaire has 33 scored items that ask about sleep habits in a typical week and are rated on a three-point scale (rarely/sometimes/usually). In addition to a total score, scores are provided for 8 subscales: bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, parasomnias, sleep-disordered breathing, night wakings, and daytime sleepiness. The CSHQ is well-validated and has strong psychometric properties among typically developing children (Owens et al., 2000). For children with ASD, modifications to the CSHQ are proposed (Katz et al., 2018).

3. Sleep disturbance and neurodevelopmental disorders

Children with NDDs have higher rates of virtually all sleep problems than TD children (Robinson-Shelton & Malow, 2016). These include difficulties falling asleep, night wakings, and parasomnias (e.g. Richdale, Gavidia-Payne, Francis, & Cotton, 2000; Quine, 1991; Quine, 2001; Wiggs & Stores, 1996). Early studies of sleep problems among children with intellectual disability (ID) show that sleep problems (particularly bedtime resistance and night wakings) are common, some forms of parasomnias (enuresis and head banging) are prevalent relative to peers, and for most children, sleep problems persist for years (Quine, 1991; Quine, 2001).

Recent studies evaluate specific forms of NDD separately, and demonstrate that sleep disturbance is pervasive across NDDs, including cerebral palsy, fragile X syndrome, Williams syndrome, and more (e.g., Angriman, Caravae, Novelli, Ferri, & Bruni, 2015; Ashworth, Hill, Karmiloff-Smith, & Dimitriou, 2013; Stores, 2014). Here, we focus on sleep disturbance in ASD, DS, and FASD. Research to date indicates that sleep disturbance is significant in these populations. Substantial research on sleep in ASD has emerged in recent years. In this paper, we compare sleep disturbance in ASD, often an idiopathic condition of unknown etiology, with sleep disturbance in a genetic condition (DS). Although sleep disturbances are present across many genetic conditions, we focus here on DS due to a relatively large body of research on sleep disturbance and on associations between sleep disturbance and functional impairment among children with DS. Finally, we compare sleep

disturbance in both conditions to FASD. Although less is known about sleep in FASD, available research highlights possible neurobiological underpinnings of sleep disturbance and is relevant for exploring possible mechanisms of sleep disturbance. It is our hope that this paper encourages further sleep research in FASD and highlights lingering questions. Comparing and contrasting findings from these disorders allows us to (1) explore transdiagnostic and diagnosis-specific disturbances in sleep among those with NDDs, (2) speculate about mechanisms of impairment, and (3) suggest avenues for future research.

3.1 Autism spectrum disorder

ASD is a NDD characterized by social communication impairments and restricted and repetitive behaviors (APA, 2013). Sleep problems are common in ASD, with most parent-report estimates higher than 50%, and as high as 86% (e.g., Krakowiak, Goodlin-Jones, Hertz-Picciotto, Croen, & Hansen, 2008; Liu, Hubbard, Fabes, & Adam, 2006; Malow et al., 2016; Souders et al., 2009). Insomnia (difficulty falling asleep, night wakings) is especially common. Caregivers of young children with ASD or developmental delay (DD) are more likely to report sleep problems than caregivers of children with TD (Krakowiak et al., 2008). Children with ASD or DD experience greater difficulty with sleep onset, but children with ASD also experience night wakings, including screaming and nightmares. Furthermore caregivers of young children with ASD or DD report greater effects of sleep problems on family function. Some reports also suggest elevated rates of parasomnias in ASD; it is unknown to what extent episodes of night wakings may reflect parasomnias among minimally verbal children (Richdale & Schreck, 2009).

Sleep problems in ASD may change with development, with fewer reports of insomnia and increased reports of daytime sleepiness by adolescence (Goldman et al., 2012). This shift may reflect developmental change or changes in caregiver perception. Youth with ASD may also experience sleep disturbance regardless of whether caregivers report concerns. In a study of adolescents with ASD, actigraphic data did not differentiate between those with or without sleep concerns; rather, the entire sample had elevated sleep parameters relative to norms, including increased sleep latency, number of night wakings, and decreased sleep efficiency (Wiggs & Stores, 2004).

Polysomnography (PSG) studies identify changes in sleep architecture in ASD. Adults with ASD show less total sleep time, differences in stage shifts, REM sleep, decreased rates of sleep spindles, and higher rates of periodic leg movement syndrome (PLMS; Godbout, Bergeron, Limoges, Stip & Mottron, 2000; Limoges, Mottron, Bolduc, Berthiaume, & Godbout; 2005). One study revealed REM sleep abnormalities (short latency, increased muscle activity, REM activity in N2) in those with ASD (Godbout et al., 2000). The other did not confirm REM findings, but longer sleep latency, less sleep efficiency, more wakefulness after sleep onset, and decreased SWS, were present in adults with ASD relative to controls (Limoges et al., 2005). Neither of these studies included individuals with comorbid ID.

Some studies have explored sleep architecture in children with ASD. Multiple studies report decreased sleep efficiency in children with ASD, as seen in adults and adolescents (e.g., Allik et al., 2006; Maski et al., 2015). Another study showed that children with ASD had

less sleep time, a higher percentage of SWS, and a lower percentage of REM sleep than children with DD or TD (Buckley et al., 2010). Children with ASD spent more time in N1 sleep than their DD peers. There were no differences in sleep architecture between the DD and TD groups. However, sample size was modest, the age range was wide, and there was no medication exclusion. The finding that children with ASD spend more time in SWS than controls runs contrary to other reports in children and adults (Lambert et al., 2013, 2016; Limoges et al., 2005).

In a more tightly controlled study, Malow et al. (2006) reported decreased REM sleep in ASD. Children with ASD classified as “poor sleepers” by their parents experienced decreased REM sleep relative to children with ASD classified as “good sleepers”. “Poor sleepers” also had decreased sleep efficiency, increased sleep latency, and increased percentage of SWS relative to “good sleepers” with ASD. However, these differences were no longer significant on the second night of PSG. Other REM abnormalities have been noted in children with ASD. Among a group of 3–9 year-old children referred for sleep evaluation due to night wakings, REM sleep disorder was present in almost half (Thirumalai et al., 2002). However, these findings may not generalize to the broader ASD population. Increased rates of REM sleep disorder have not been reported in other PSG studies. Overall, studies of ASD in adults and children raise the possibility that REM sleep is altered. The nature of REM disturbance varies, possibly due to differences in exclusion criteria, small samples, or age differences. Differences in REM sleep and other aspects of sleep architecture may also derive from heterogeneity in ASD diagnoses and etiopathophysiologies.

In addition to altered macrostructure of sleep (sleep stages), changes in microstructure are observed in ASD (Bruni et al., 2007; Miano et al., 2007). Adolescents and adults with ASD generate fewer sleep spindles (Godbout et al., 2000; Limoges et al., 2005). So far, at least two studies suggest that children with ASD show reduced sleep spindle density (Lambert et al., 2013; Tessier et al., 2015). Furthermore, Tessier et al. reported that sleep spindle density was correlated negatively with verbal and full-scale IQ among children with ASD (none of whom had sleep concerns). However, aforementioned samples only included individuals with ASD without comorbid ID. Limited findings in those with ASD and ID suggest greater spindle activity, present even in REM (Diomedi et al., 1999), consistent with early reports of “extreme spindles” in ID (Gibbs & Gibbs, 1962). In typical development, sleep spindles are proposed as an index of intelligence, with a possible curvilinear association between spindle activity and IQ (Fogel & Smith, 2011). Therefore, it is possible that intellectual functioning in NDDs moderates differences in sleep spindle activity.

Cyclic alternating pattern (CAP) analysis provides an index of sleep stability in NREM (see Bruni et al., 2010). Children with ASD and ID show lower CAP rates in SWS than controls (Miano et al., 2007). In general, lower CAP rates indicate sleep stability. However, further analysis of CAP subtypes provides additional information. A1 subtypes protect and maintain deep sleep, whereas A2 and A3 subtypes reflect arousal or preparation for arousal (Bruni et al., 2010). Although children with ASD and ID have lower overall CAP rates, they show decreases in A1 percentage and increases in A2 and A3 percentages (Miano et al., 2007). In contrast, youth with ASD without ID exhibit multiple differences in microstructure

compared with youth with comorbid ID, and TD youth (Bruni et al., 2007). Notably, CAP parameters in ASD without ID correlate with verbal and nonverbal IQ scores, providing further evidence that heterogeneity of sleep microstructure in ASD may relate to IQ and/or comorbid ID.

3.2 Down syndrome

Down syndrome (DS) is a genetic condition that affects structure and function of multiple body systems, including the brain, resulting in ID (Churchill, Kieckhefer, Landis & Ward, 2012). DS is often caused by trisomy of the 21st Chromosome. Those with DS often experience obstructive sleep apnea (OSA). Prevalence estimates of OSA range from 50–80%, with further breathing-related abnormalities noted on PSG in almost all children (e.g., Angriman et al., 2015; Ashworth et al., 2013; Austeng et al., 2014; Shott et al., 2006). Craniofacial and upper airway abnormalities, hypotonia, and obesity associated with DS confer vulnerability to OSA (e.g., Churchill et al., 2012). Typical treatment for OSA in children is adenotonsillectomy—removal of the tonsils and/or adenoids. However, this procedure is less effective for children with DS given additional physical factors that obstruct breathing (Best, Mutchnick, Ida, & Billings, 2018; Dorris, Scott, Zuberi, Gison, & Espie, 2008).

In a study of more than half of all 8-year-old children born with DS in Norway in 2002, all but one had at least mild sleep apnea according to PSG data, and 2/3 fell in the moderate to severe range (Austeng et al., 2014). Although some had their tonsils and/or adenoids removed due to frequent infections, there were no differences between children with and without surgery on OSA. None had prior diagnoses or referrals, underscoring unmet need in this population.

Children with DS often experience hypertension and cardiovascular complications, which are exacerbated by OSA (e.g., O'Driscoll, 2009). Therefore, given the high prevalence of OSA in DS, some argue that all children with the disorder be evaluated (e.g., Shott, 2006). Guidelines from the American Academy of Pediatrics recommend that all families of children with DS receive information about OSA symptoms within the first six months of childhood, and that children undergo routine screening (Bull & the Committee on Genetics, 2011).

Most of the literature on sleep disturbance in DS focuses on OSA, but other forms of sleep disturbance are present. Children with DS may be at-risk for other forms of sleep-disordered breathing, such as central sleep apnea (e.g., Trucco et al., 2018). In addition, parents of school-age children with DS report elevated bedtime resistance, sleep anxiety, night wakings, parasomnias, and daytime sleepiness (Ashworth et al., 2013; Carter, McCaughey, Annaz, & Hill, 2009). Although some symptoms may be manifestations of OSA, children with DS experience sleep fragmentation and architecture changes beyond what can be attributed to OSA (e.g., Nisbet, Phillips, Hoban, & O'Brien, 2015). Children with DS show decreased sleep efficiency (Fernandez et al., 2017). Furthermore, in a large study of children referred to a sleep center, those with DS spent more time in SWS and less time in REM and N2 sleep than controls (Nisbet et al., 2015). These differences were found among children as

young as 2-years-old, and remained when those with OSA were excluded. These findings are consistent with findings from non-referred adolescents (Miano et al., 2008).

Decreased N2 sleep raises the question of whether sleep spindle activity is impaired in DS, but limited research is available. In an early study, Clausen, Sersen, and Lidsky (1977) found "sparse" sleep spindles in individuals with DS. They compared institutionalized adolescents and young adults with a comparison group of caregivers from the same institution. Finally, similar to microstructure findings from children with ASD and comorbid ID, Miano and colleagues (2008) found decreased A1 percentage and increased A2/A3 percentage. Overall, the suggestion that children with DS have altered sleep architecture, beyond increased rates of sleep-disordered breathing, warrants further study.

3.3 Fetal alcohol spectrum disorder

FASD is an umbrella term used to describe those who experience neural dysfunction related to prenatal alcohol exposure (see Doyle, Crocker, Fryer, & Mattson, 2017). It is synonymous with the term *neurobehavioral disorder associated with prenatal alcohol exposure* (ND-PAE; APA, 2013), and includes fetal alcohol syndrome, partial fetal alcohol syndrome, and alcohol-related neurodevelopmental disorder. Children with FASD experience substantial sleep disturbance (Hanlon-Dearman, Chen, & Olson, 2018; Inkelis & Thomas, 2018; Ipsiroglu et al., 2019). Fragmented sleep is seen as young as age 6 weeks (Troese et al., 2008). In a longitudinal study in Finland, prenatal alcohol exposure predicted almost three-fold risk for short sleep duration and more than three-fold risk for decreased sleep efficiency by 8 years of age (Pesonen et al., 2009).

Wengel, Hanlon-Dearman and Fjeldsted (2011) examined sleep problems among preschool children with FASD, who were in stable foster homes. Sleep problems were measured with the CSHQ (Owens, Spirito, & McGuinn, 2000), and actigraphy. Almost every functional domain assessed by the CSHQ was elevated, with parents noting significant sleep problems such as roaming the house at night. However, actigraphic data revealed only longer sleep onset latency. Actigraphic data may not be sensitive enough to detect night wakings (Sitnick, Goodlin-Jones, & Anders, 2008). Alternatively, questionnaires may capture distress experienced by families, as children's disturbed sleep can disrupt sleep for the entire family.

In research among school-age children, Chen and colleagues (2012) compared those with FASD with community controls from the original CSHQ study. Most of children in the FASD group (85%) had elevated total scores on the CSHQ compared with 35% of controls. The FASD group showed disrupted scores in every sleep domain. On average, children with FASD slept an hour less than their peers. A very small subset of five children with FASD and elevated CSHQ scores completed a PSG evaluation. These children exhibited elevated total arousal, suggesting fragmented sleep, and elevated apnea-hypopnea indices, suggesting respiratory disturbances. These elevations were due primarily to obstructive events rather than central events.

A recent study using PSG in a larger sample of youth with FASD, ages 6–18 years, confirmed significant sleep disturbance (Goril, Zalai, Scott, & Shapiro, 2016). Participants had lower sleep efficiency and increased sleep fragmentation relative to published norms.

More than two-thirds (78%) had significant or sub-threshold disturbance on PSG, and 58% met criteria for a sleep disorder. Parasomnias were most common (28%). This study did not include a control group so it is unclear if parasomnia rates are elevated relative to children with TD, or if rates decrease with age as would be expected. Consistent with preliminary findings from Chen et al. (2012), about 10% of youth had OSA (compared to 1–4% of TDs; AASM, 2014). A subset of the sample completed the dim light melatonin onset test. Nearly 80% exhibited abnormal melatonin secretion, indicating significant potential for circadian disturbance in FASD.

4. Associations between sleep disturbance and daytime function in NDDs

Getting enough quality sleep is critical to healthy development. Correlational and experimental studies among children with TD demonstrate associations between both sleep quantity and quality and daytime function, including sleepiness, school performance, attention, impulse control, mood, and behavior regulation (e.g., Baum et al., 2014; Beebe, 2011; Gruber, Cassoff, Frenette, Wiebe, & Carrier, 2012; Vriend et al., 2013). Fatigue, poorer cognitive performance, and changes to mood, and behavior are evident even with modest sleep restriction of less than an hour per night (Gruber et al., 2012; Sadeh, Gruber, & Raviv, 2003). Here, we focus on findings specific to NDD populations. Most research conducted to date has focused on ASD or general ID, with some research in DS, and almost no studies addressing FASD.

4.1 Behavior problems

Early studies of children with various forms of ID, including ASD and DS, show more intense and frequent behavior problems among those with concurrent sleep problems (e.g., Quine, 1991; Richdale et al., 2000; Wiggs & Stores, 1996). Among children with mild to profound ID, those with severe sleep problems exhibit higher scores across nearly all behavior problem domains (Didden, Korzilius, van Aperlo, van Overloop, & de Vries, 2002). Findings linking sleep problems to behavior problems among children with NDDs are consistent (e.g., Goldman et al., 2011; Johnson et al., 2018; Mazurek & Sohl, 2016; Rzepecka, McKenzie, McClure, & Murphy, 2011). Children with DS and sleep problems show more behavior problems, including irritability, inattention and hyperactivity/impulsivity (Esbensen, Hoffman, Beebe, Byars, & Epstein, 2018; Stores, Stores, Fellows, & Buckley, 1998). A pilot study of young children with FASD (ages 3 to 7 years) demonstrated an association between sleep duration and behavior problems (Mughal & Dimitriou, 2017). In a large study of children with ASD and their unaffected siblings, evidence of any sleep problem from the CSHQ predicted higher internalizing, externalizing, and total behavior problem scores in the ASD group (Park et al., 2012). Such associations are among the most consistent findings in the ASD sleep literature (Hollway & Aman, 2011). Among youth with ASD, short sleep duration is also associated with psychiatric comorbidities, including attention-deficit/hyperactivity disorder (ADHD), depressive disorder, and obsessive-compulsive disorder (Veatch, 2017).

Cohen et al. (2018) used supervised machine learning methods to examine whether sleep predicted daytime behavior among youth with ASD living in residential facilities, and

whether additional nights of sleep (up to two weeks prior) improved prediction. Staff conducted regular checks (15–30 min) between “lights off” and “lights on” and recorded whether individuals were asleep or awake. During the daytime, staff recorded hourly whether individuals engaged in aggression, self-injury, tantrums, and/or property destruction. Although prior night’s sleep predicted daytime behavior, prediction accuracy was highest when considering additional nights’ sleep. The prior week’s sleep (across 8 days) predicted daytime behavior with accuracy greater than chance for 81% of youth. Variability in sleep patterns, such as timing and duration, most consistently predicted behavior. Abel and colleagues (2018) also found that average sleep duration, across multiple nights, predicted behavior problems among young children receiving intensive behavioral intervention. Mazurek and Sohl (2016) examined aspects of sleep that predict behavior problems among children with ASD from ages 3 to 19 years. Sleep duration, sleep anxiety, parasomnias, night wakings, and daytime sleepiness were associated with behavior problems. Night wakings and parasomnias exerted particularly strong effects. When combined with daytime sleepiness, they explained 31% of the variance in hyperactivity symptoms.

4.2 Caregiver stress

Children’s sleep problems should be viewed within a family context as they often affect siblings and caregivers. Multiple studies in ASD, and some in DS, find correlations between caregiver stress and children’s sleep problems (e.g., Doo & Wing, 2006; Johnson et al., 2018; Quine, 1991; Richdale et al., 2000; Stores et al., 1998). Doo and Wing surveyed caregivers of young children with ASD. A majority of caregivers (82.6%) reported elevated stress levels, and their report of stress correlated with CSHQ total scores, indicating that caregivers of those with sleep problems had even greater stress. Parents frequently report fatigue and co-sleeping as consequences of children’s sleep problems (Didden et al., 2002). On average, parents of children with ASD sleep an hour less per night (Meltzer, 2008). Disruptions to caregiver sleep may mediate the association between sleep problems and caregiver stress (Meltzer & Montgomery-Downs, 2011). Effective behavioral treatment can have a positive effect on parents, including increased sleep, reduced stress, and increased perceived control regarding children’s sleep (Wiggs & Stores, 1998; Wiggs & Stores, 2001).

4.3 Adaptive behavior and symptom severity

Taylor et al. (2012) examined relations between sleep problems and adaptive behavior among children with ASD. Children who slept fewer hours (including naps) had poorer overall adaptive function, socialization skills, daily living skills, and motor skills. Children who slept more were less sensitive to their environments, less likely to wake up screaming, and had higher communication scores. Data from a large national database also support an association between sleep duration and adaptive communication (Hollway et al., 2013). Furthermore, in a residential treatment setting, youth with unstable sleep patterns demonstrated poorer adaptive behavior than those with stable sleep patterns (Cohen et al., 2017). In youth with DS, parent-reported sleep problems, such as bedtime resistance, night wakings, and sleep duration predicts lower adaptive behavior (Churchill, Kieckhefer, Bjornson, & Herting, 2015). Objective sleep parameters of sleep efficiency, daytime

sleepiness, and total time spent in SWS also correlate with adaptive behavior in DS (Brooks et al., 2015).

ASD severity is also related to sleep problems. Among school-age children, sleep problems are associated with greater ASD symptoms (Schreck, Mulick, & Smith, 2004). Fewer hours of sleep predict ASD severity scores, social skill deficits, and stereotypic behaviors. Communication problems correlate with sensitivity to stimuli in the sleep environment and periods of night screaming. Many of these findings derive from rating scales of ASD; however, associations between sleep and symptom severity hold with gold standard ASD evaluations (Park et al., 2012; Veatch et al., 2017). Among youth with ASD, bedtime resistance, insomnia, and daytime sleepiness predict stereotyped behaviors, and bedtime resistance predicts poor communication (Park et al., 2012). Furthermore, short sleep duration predicts increased ASD severity, including both social impairment and repetitive, restricted behaviors (Veatch et al., 2017). Thus, sleep problems are associated with core ASD symptoms—not just comorbid behavior problems.

Few prospective studies examine longitudinal associations between ASD symptoms and sleep problems (e.g., Nguyen, Murphy, Kocak, Tylavksy, & Pagani, 2018; Verhoeff et al., 2018). Findings regarding whether sleep problems precede and intensify ASD symptoms are mixed. Nguyen et al. reported that night wakings in infancy predicted increased ASD symptoms one year later (albeit with a small effect size). However, Verhoeff et al. reported that longitudinal associations did not remain after controlling for early ASD symptoms. Both studies were limited by measurement selection—an understandable methodological challenge in such large samples (N>1,000). Further prospective investigations with stronger methods of sleep and ASD assessment would be beneficial for disentangling temporal associations between sleep disturbance and ASD symptomatology. Regardless, it does appear that sleep problems emerge early and persist over time for children with ASD (Humphreys et al., 2014; Verhoeff et al., 2018).

4.4 Cognitive function

The literature on associations between sleep problems and intelligence in ASD is mixed (Hollway & Aman, 2011). Some studies show an association (Cohen et al., 2017; Hollway et al., 2013; Taylor, Schreck, & Mulick, 2012; Veatch et al., 2017) whereas others do not (Cortesi, Giannotti, Ivanenko, & Johnson, 2010; Johnson et al., 2018; Mayes & Calhoun, 2009). One study of school-age children with ASD without ID demonstrated that, proportion of N1 correlates inversely with IQ (Lambert et al., 2016). It is possible that associations between sleep and IQ are present only within certain ranges of IQ, or relate to presence of ID. Mixed findings exist regarding associations between sleep problems and ID severity (Didden et al., 2002; Richdale et al., 2000); however, the presence of ID is associated with increased sleep problems in ASD (Cohen, Conduit, Lockley, Rajaratnam, & Cornish, 2014; Johansson, Feeley, Dorman, & Chasens, 2018). In a meta-analysis of sleep problems in ASD, inclusion of children with ID moderated differences in total sleep time; those with ID had greater differences in TST from TD controls than those without ID (Elrod & Hood, 2015). Therefore, associations between sleep characteristics and IQ may vary depending on whether ID is or is not present.

In DS, OSA is associated with lower verbal IQ among school-age children (Breslin et al., 2014). In addition, toddlers with DS and poor sleep efficiency use fewer words, are less likely to combine words, and use shorter sentences than toddlers with adequate sleep efficiency (Edgin et al., 2015). School-age children with DS also show poor sleep-dependent learning on verbal naming tasks (Ashworth, Hill, Karmiloff-Smith, & Dimitriou, 2017). Thus, sleep disturbance in DS is related to language impairment and verbal learning. Preliminary data suggests that sleep duration and language skills are also correlated in FASD (Mughal & Dimitriou, 2017). This possibility should be evaluated in ASD given language impairments observed in the disorder.

Some have speculated that high rates of OSA and sleep fragmentation in DS may contribute to cognitive impairment and early onset of dementia (Breslin et al., 2014; Fernandez & Edgin, 2013). REM sleep percentage and time spent in SWS are associated strongly with cognitive abilities in DS (e.g., Brooks et al., 2015). Children with DS and OSA spend less time in SWS and more time in N1 sleep than those without OSA (Breslin et al., 2014). However, it is difficult to reconcile these findings with those of Nisbet et al. (2015), who found that children with DS spend more time in SWS than their TD peers. Additional PSG studies in DS may clarify these findings and determine whether this may vary based on additional sleep variables.

Whether sleep disruption interferes with learning and memory in DS, and what type of sleep disruption may so interfere, are interesting questions that require further research. For example, Joyce and Dimitriou (2017) did not find associations between SDB and developmental or behavioral function in children with DS, although they did find associations in their TD peers. Findings from adults with DS also suggest that behavioral sleep disturbance and OSA may have distinct correlates (Esbensen, 2016). This line of inquiry deserves further exploration.

Taken together, these studies indicate clear associations between sleep disturbance and functional impairment for those with NDDs. Sleep disturbance is associated, not only with comorbid symptoms, but with core features of NDDs. Further research is needed to enrich these findings—particularly for FASD—which is underrepresented in this literature.

5. Abbreviated neurobiology of sleep

Before discussing possible mechanisms of sleep disturbance in NDDs, it may be helpful to briefly review sleep neurobiology. Neurobiological mechanisms of sleep, coupled with pathophysiological mechanisms of specific NDDs, provide clues to possible sources—both transdiagnostic and disorder-specific—of sleep difficulties in ASD, DS, and FASD.

5.1 Implicated neural systems

Sleep processes, including shifting among stages, are subserved by dynamic interactions among multiple brain regions and neurotransmitter systems. The hypothalamus, brainstem, and basal forebrain are important regions for sleep regulation (España & Scammell, 2011; Wright, Lowry, & LeBourgeois, 2012). Implicated neurotransmitters include acetylcholine

(ACh), γ-aminobutyric acid (GABA), glutamate, orexin, and several monoamines (e.g., norepinephrine [NE], histamine [HA], serotonin [5-HT], dopamine [DA], and melatonin).

There are high concentrations of ACh in the brainstem and basal forebrain, which promote wakefulness and increased cortical activity during REM (España & Scammell, 2011). ACh neurons project to the thalamus, which integrates inputs from multiple sensory systems. GABAergic neurons in the basal forebrain increase cortical activation by inhibiting modulating inhibitory cortical interneurons, whereas excitatory glutamatergic neurons in the basal forebrain increase wakefulness (Wright et al., 2012). In general, monoamines increase wakefulness, are less active during NREM, and least active during REM. For DA, extracellular levels are highest during wakefulness and lowest during NREM (España & Scammell, 2011). Evidence that DA modulates sleep and wakefulness comes from medication effects; DA agonists reduce fatigue, whereas DA antagonists induce fatigue.

Finally, orexin is a neuropeptide that projects to multiple brain structures, including the LC, the TMN, and the cortex, from the lateral hypothalamus (España & Scammell, 2011). Similar to monoamines, orexins are more active during wake. Narcolepsy with cataplexy is associated with significant loss of orexin neurons and signaling (Nishino et al., 2000). Orexins may also help to maintain and stabilize sleep, a hypothesis derived from fragmented sleep observed in narcolepsy.

5.2 Role of thalamocortical loops

The thalamus plays a critical intermediary role between subcortical and cortical structures (España & Scammell, 2011). Thalamic glutamatergic neurons relay sensory information to the cortex, whereas GABAergic neurons inhibit relay of sensory information (e.g., decreased sensory awareness during sleep). These thalamocortical loops may drive some cortical rhythms observed in EEGs, including sleep spindles (Fogel & Smith, 2011).

5.3 Non-REM sleep

The preoptic area is another region of the hypothalamus that promotes sleep. Neurons in the ventrolateral preoptic area (VLPO) are thought to maintain sleep and neurons in the median preoptic area (MNPO) are thought to initiate sleep (España & Scammell, 2011; Wright et al., 2012). One of the prominent neurotransmitters in this region is the inhibitory neurotransmitter GABA. These areas are thought to initiate and sustain sleep, at least in part, by inhibitory projections from GABAergic neurons to the arousal-promoting regions (e.g. LC, etc.). Thalamic neurons are also hyperpolarized during this time resulting in reduced responsiveness to sensory input and the deeper waves that are characteristic of NREM sleep.

5.4 REM sleep

Cholinergic neurons in the pons play a critical role in managing REM sleep (España & Scammell, 2011). ACh serves to depolarize the neurons in the thalamus, in order to increase thalamocortical signaling. The cholinergic neurons also signal to inhibitory neurons, including GABA, in the ventromedial medulla. This inhibition, in combination with the withdrawal of excitatory monoamines such as NE and 5-HT creates the muscle paralysis that is characteristic of REM sleep. Animal models have demonstrated that enhancing ACh

activity leads to long-lasting REM sleep, while lesions to this area substantially reduce and almost eliminate REM sleep (e.g. Nguyen, Liang, & Marks, 2013; Webster & Jones, 1988). Orexins also play a role in suppressing REM sleep by exciting the monoaminergic systems. Therefore, low orexins in narcolepsy may be the neurobiological basis for REM instrusions into waking hours. Serotonin may also play an important role in suppressing REM as serotonin agonists reduce REM (Mayers & Baldwin, 2005).

5.5 Two-process model of sleep

Two broad processes are proposed to regulate the sleep-wake cycle (Borbély, Daan, Wirz-Justice, & Deboer, 2016). Process 'S' is homeostatic and increases desire to sleep as wake continues. Infants and children have a stronger homeostatic drive to sleep than adults, thus creating difficulties in sustaining wakefulness (Mindell & Owens, 2015). Process 'C' is circadian, following a 24-hour rhythm.

The "master clock" for regulating circadian rhythms is located in the suprachiasmatic nucleus (SCN) of the hypothalamus (Wright et al., 2012). However, circadian clocks are also present in virtually all cells of the body (Mindell & Owens, 2015). SCN neurons innervate many regions described above, synchronizing circadian arousal cycles. The SCN also regulates melatonin release from the pineal gland (Rajaratnam et al., 2009). Melatonin, released primarily at night, is a monoamine neurohormone that initiates sleep and is critical for the process of *entrainment,* which humans require to synchronize to 24-hr cycles (Duffy & Czeisler, 2009). *Zeitgebers* are external cues that guide entrainment (Elmore, Betrus, & Burr, 1994). The primary zeitgeber is light; visual daylight information is processed by the hypothalamus, which helps guide sleep-wake cycles. Other zeitgebers include timing of meals and social routines.

6. Possible mechanisms of sleep disruption in NDDs

6.1 Behavioral factors

For children with NDDs, similar to TD children (Moore, Meltzer, & Mindell, 2008), behavioral factors can initiate and maintain sleep disturbance. Poor sleep hygiene, such as lack of a consistent sleep schedule can induce insomnia (Moss, Gordon, & O'Connell, 2014), and children with ASD may have poorer sleep hygiene than TD children (van der Heijden, Stoffelsen, Popma, & Swaab, 2018). For children with ASD, who show restricted and repetitive behaviors, perseveration at bedtime can lead to bedtime resistance and difficulty settling (Richdale & Schreck, 2009). Increased caregiver stress among families of children with NDDs may lead to difficulty providing structure around sleep. Inadequate limit setting, as with children with TD, can elicit bedtime resistance and night wakings. As outlined above, children with NDDs experience elevated rates of behavior problems, which are associated with sleep problems (e.g., Goldman et al., 2011; Rzepecka et al., 2011). Behavior problems at night may interfere with parents' limit setting, thus contributing to sleep problems. For children with FASD, there are often additional environmental stressors, such as parental substance use disorders or placement with foster families (Olson, Jirikowic, Kartin, & Astley, 2007). Children with multiple placements may experience changes in sleep

habits and expectations, rather than consistency and structure. Inconsistency in sleep habits or elevated rates of anxiety resulting from these stressors can contribute to sleep problems.

6.2 Sleep-disordered breathing

In addition to behaviorally based sleep concerns, medical sleep concerns are also more common among children with NDDs. This includes sleep-disordered breathing, which is prominent among children with DS (see above), and is also experienced by at least some children with FASD (e.g., Goril et al., 2016). As outlined above, respiratory disturbances may arise from craniofacial abnormalities that are common in FASD (Chen et al., 2012). In addition, prenatal alcohol exposure in rats is associated with changes in ventilatory responses that could create vulnerabilities for sleep-disordered breathing (Dubois, Houchi, Naassila, Daoust, & Pierrefiche, 2008). In contrast, children with ASD experience OSA rates similar to their TD peers (Reynolds & Malow, 2011).

6.3 Circadian rhythm dysfunction

Some sleep difficulties in ASD may relate to abnormalities in circadian rhythms and melatonin synthesis (Cortesi et al., 2010; Geoffray, Nicolas, Speranza, & Georgieff, 2016; Reynolds & Malow, 2011). Low levels of melatonin are found consistently among individuals with ASD (Geoffray et al., 2016; Melke et al., 2008). Markers of melatonin correlate positively with SWS and negatively with caregiver-rated daytime sleepiness, indicating that children with higher levels of melatonin may experience higher quality sleep and feel more rested (Leu et al., 2011). Conversely, low melatonin may disrupt circadian rhythms and lead to difficulties falling asleep (e.g., Rajaratnam et al., 2009). Children with ASD may experience additional entrainment difficulties as a result of social deficits (e.g., Elmore et al., 1994).

Children with FASD may also experience circadian rhythm dysfunction (Goril et al., 2016). Findings from animal models of FASD also suggest circadian rhythm dysfunction is likely (see Allen at al., 2005). Changes within the suprachiasmatic nucleus, including altered clock gene oscillations, may reflect an underlying mechanism for circadian rhythm dysfunction (Farnell et al., 2008). In contrast to findings in ASD and FASD, preliminary findings suggest that circadian rhythms may be intact in DS (Fernandez et al., 2017).

6.4 Other neurobiological dysfunction

NDDs confer abnormalities in a wide range of neurobiological structures and functions that cannot all be reviewed here. Notably, the extent of these abnormalities is still being elucidated. Prenatal alcohol exposure affects brain development in myriad ways. For example, exposure can alter thalamic structure and function (e.g., Lebel et al., 2008). This suggests that sleep spindle abnormalities may be possible. Sleep spindle abnormalities observed in ASD, and to a lesser extent DS, also suggest thalamocortical disruption. This assertion was recently corroborated by findings of reduced Delta EEG activity, which reflects disrupted thalamocortical function during NREM sleep, in adults with ASD (Rochette et al., 2018).

Thalamic activity during NREM sleep gates sensory input to the cortex, with sleep spindle activity thought to reflect diminished attention to sensory input (España & Scammell, 2011). Decreased or otherwise abnormal sleep spindles may reflect underlying impairment in thalamocortical filtering. Sensory processing impairments are common to ASD and FASD, and are proposed to affect sleep negatively (Cortesi et al., 2010; Tzischinsky et al., 2018; Wengel et al., 2011). For example, if children are hypersensitive to extraneous stimuli, they may have difficulty 'tuning them out' and falling/staying asleep (e.g., Hairston et al., 2010). Another possibility is that thalamocortical dysfunction reflects a common mechanism that underlies both sleep disruption and sensory processing abnormalities.

Decreased REM sleep is a consistent finding in DS (e.g., Churchill et al., 2012; Nisbet et al., 2015). REM abnormalities are often noted in ASD, but their precise nature varies from study to study (e.g. Buckley et al., 2010; Malow et al., 2006). Furthermore, some studies of REM abnormalities in ASD include children who used medications, making it difficult to disentangle medication effects from effects of ASD itself (e.g., Buckley et al., 2010; Godbout et al., 2000). As noted above, it is possible that different subgroups of children with ASD have different patterns of REM sleep. So far, limited PSG data in FASD have not identified differences in REM sleep. However, rat models of FASD demonstrate decreased active (REM) sleep (Hilakivi, 1986; Olateju, Bhagwandin, Ihunwo, & Manger, 2017), as well as changes to the orexinergic and cholinergic systems that could reasonably alter REM sleep (Olateju et al., 2017). Thus, the possibility of differences in REM sleep needs to be examined in children with FASD as well.

Changes in sleep architecture, and other forms of sleep disturbance, could reflect disturbances in neurotransmitter function (see e.g., Mallick et al., 2002; Mazzone, Postorino, Siracusano, Riccioni, & Curatolo, 2018). One hypothesis in ASD posits that a primary cholinergic deficiency accounts for decreased REM sleep and increased SWS (Buckley, 2010). Another hypothesis from the ASD literature suggests that altered serotonin function/metabolism could cause sleep disturbance among those with ASD (see above). Hyperserotonemia is often observed in ASD (Muller, Anacker, & Veenstra-Vanderweele, 2016) and could explain reduced REM sleep, which in turn may increase SWS. Hyperserotonemia may arise from a primary deficit in melatonin synthesis (Bourgeron, 2007). Both ACh and serotonin are implicated as potential mechanisms for parasomnias (Proserpio & Nobili, 2017), which may be elevated in ASD and FASD (Richdale & Schreck, 2009; Wengel, Hanlon-Dearman, & Fjeldsted, 2011). Functional alterations to these systems may also help to explain high comorbidities with attention problems, mood disorders, and anxiety disorders, which we consider next.

6.5 Relations with other disorders?

6.5.1 Attention-deficit/hyperactivity disorder—Several NT systems important for sleep regulation (e.g., DA and ACh) are also implicated in attention regulation, including sustained attention and arousal. Children with ADHD display high rates of sleep disturbance, including difficulties with initiating and maintaining sleep (e.g., Owens, 2005; van der Heijden et al., 2018). Comorbid diagnoses of ADHD are common in ASD (~28%; Simonoff et al., 2008), DS (~44%; Ekstein, Glick, Weill, Kay, & Berger, 2011), and FASD

(as high as 70%; Greenbaum, Stevens, Nash, Koren, & Rovet, 2009). In addition, comorbid diagnoses of ADHD are associated with sleep problems in ASD (Veatch et al., 2017). We speculate that this could implicate common neural pathways and other mechanisms of sleep disturbance in ADHD and at least some cases of NDD.

Children with ADHD experience high rates of restless leg syndrome and PLMS (Owens, 2005). One partial mechanism may be low iron, which, as a cofactor for dopamine, could contribute to low dopamine levels (Konofal, Lecendreux, & Cortese, 2010). Increased rates of PLMS are also present in ASD (e.g., Godbout et al., 2000). Children with ADHD also show more general body movements during sleep, as detected by infrared cameras (Konofal, Lecendreux, Bouvard, & Mouren-Simeoni, 2001). Given these findings, Konofal et al. (2010) suggest that ADHD is a “24 hour disorder” with hyperactivity continuously present and interfering with sleep. This may apply to certain NDDs populations as well; structural and functional neurobiological causes of daytime symptoms of NDDs may alter sleep behavior.

Similar to findings in ASD and FASD, circadian rhythm dysfunction is a consistent finding in ADHD (Coogan & McGowan, 2017). Children with ADHD experience delayed sleep onset, corroborated by delayed release of melatonin. As in FASD research, alterations to clock genes are being explored as potential mechanisms. In addition, Xia et al. (2012) suggest that abnormalities in thalamic structure and connectivity may be implicated.

6.5.2 Anxiety and depression—Mood and anxiety disorders are common among children with ASD and FASD (e.g., Hellemans, Sliwowska, Verma, & Weinberg, 2010; Hollocks, Howlin, Papadopoulos, Khondoker, & Simonoff, 2014). Although rates of anxiety are not as high in DS, those with DS experience high rates of depression (Dykens, 2007). Anxiety disorders and depression are often accompanied by sleep disturbance, including insomnia, nightmares, and night terrors (Dahl & Harvey, 2007). Those with endogenous depression in particular experience shorter REM latency (e.g., Dahl & Harvey, 2007). Serotoninergic dysfunction has long been implicated in both depression and suppressed REM sleep (España & Scammell, 2011). Shortened REM latency may reflect a failure to normally suppress REM sleep. SSRIs, which increase serotonin activity and reduce REM, may normalize sleep among such individuals (see Mayers & Baldwin, 2005).

PSG findings among anxious youth include more night wakings, less SWS, longer sleep onset latency, and reduced latency to REM (Alfano, Reynolds, Scott, Dahl, & Mellman, 2013; Forbes et al., 2008). For those who are anxious, sleep disturbance may result from difficulties shifting attention away from worries and rumination (Peterman, Carper, & Kendall, 2015). Physiologically, elevated cortisol at bedtime may indicate an increased stress response (Forbes et al., 2008). The limbic-hypothalamic-pituitary-adrenal (L-HPA) axis, which releases cortisol in response to stress, is often dysregulated in anxiety and depression.

L-HPA axis dysregulation is also common to children with FASD and children with ASD and comorbid anxiety (Hellemans et al., 2010; Hollocks et al., 2014). L-HPA axis dysregulation may interfere with sleep initiation and contribute to symptoms of insomnia in NDDs, as among anxious and depressed youth. However, this mechanism is speculative at

present. Magnetic resonance imaging (MRI) studies of FASD reveal decreased hippocampal volumes, which are also associated with abnormal L-HPA axis responding (Astley et al., 2009). The hippocampus serves a homeostatic stress response function by detecting circulating cortisol and terminating the stress response (Stokes, 1995). Decreased hippocampal volumes among those with FASD, ASD, and DS may be associated with L-HPA axis dysregulation (e.g. Aylward et al., 1999; Fernandez et al., 2017).

We speculate that changes to hippocampal function and L-HPA axis may alter stress responding in NDDs, and in turn, sleep regulation. However, it should be noted that L-HPA axis function is affected by top-down influence by the prefrontal cortex (PFC), and that both sleep and L-HPA axis disruption among those with anxiety disorders may be both causes and consequences of weakened PFC regulation (Dahl, 1996; Peterman et al., 2015). This possibility needs to be investigated in NDDs as PFC abnormalities are also implicated in ASD (e.g., Mazefsky et al., 2013), DS (e.g., Edgin, 2013), and FASD (e.g., Uban et al., 2011).

6.6 Additional factors

Other factors may prevent quality sleep, including comorbid medical concerns (e.g., asthma, allergies, epilepsy; see Reynolds & Malow, 2011). GI disturbances predict sleep problems among children with ASD (Hollway et al., 2013; Krakowiak et al., 2008). Several studies also demonstrate that pain interferes with sleep in children with ASD and other NDDs (e.g., Tudor, Walsh, Mulder, & Lerner, 2014). Chronic pain is associated with parasomnias (Tudor et al., 2014). Regardless of diagnostic status, pain sharpens attention, increases arousal, and fragments sleep—known triggers for parasomnia (Ekambaram & Maski, 2017).

NDDs are treated with various psychoactive medications, including stimulants, anti-psychotics, antidepressants, and others. Many of these alter sleep (Blackmer & Feinstein, 2016). For example, stimulants may lead to difficulty falling asleep. Although effects of antipsychotics on sleep architecture are not yet known, many extend the length of sleep. As mentioned above, antidepressants suppress REM sleep. For children with increased REM, this may normalize their sleep. In contrast, if children experience decreased REM, as in DS, and possibly for some with ASD, these medications may further impair sleep quality.

7. Summary and implications

Sleep difficulties are prevalent in NDDs, including ASD, DS, and FASD. However, sleep disturbance is not specific to NDDs, and associations with common comorbidities, including internalizing and externalizing symptoms, are similar for those with and without NDDs. It may be fruitful to examine transdiagnostic behavioral and neural processes associated with sleep disturbance. To date, most research has been descriptive, verifying patterns of sleep disturbance but not identifying mechanisms. We argue that enough is known about sleep physiology for more mechanistic research. Understanding sleep disturbance may elucidate etiological mechanisms of NDDs. For example, by studying children with ASD and delayed sleep onset, Veatch et al. (2015) identified associated melatonin pathway genes.

In our comparison of ASD, DS, and FASD, we identified diagnosis-specific (e.g., OSA in DS) and transdiagnostic (e.g., poor sleep efficiency) features of sleep disturbance. Moreover, findings from ASD and DS suggest avenues for future research on FASD, where relatively few studies have been conducted. In particular, altered sleep architecture, such as changes to SWS, REM, and sleep spindles may be present in FASD based on findings from ASD and DS.

It is important to emphasize that many relations between sleep disturbance and NDD symptoms are bidirectional. Inadequate sleep quantity or quality can result from and induce symptom intensification, cognitive performance deficits, and behavior problems. This of course suggests that sleep disturbance may improve through successful interventions for core symptoms, and that successful interventions for sleep disturbance may improve core symptoms.

Our understanding of sleep disturbance in NDDs is limited by small samples, variability in inclusion/exclusion criteria, overreliance on parent report, and inconsistent use of validated sleep measures. Inconsistent inclusion and exclusion criteria make it difficult to parse which features of sleep disturbance are characteristic of NDDs and which are due to outside factors, such as medication use. Studies with more stringent exclusion criteria are better equipped to attribute group differences to specific NDDs. These issues could be addressed through multi-site collaborations, which standardize measurement and increase sample size.

In addition, most studies conducted to date are cross-sectional, yet sleep patterns change markedly across development (e.g., McCarley, 2007). Unlike normal patterns of sleep development, however, our knowledge about sleep maturation among those with NDDs is limited, with some exception (e.g., Goldman et al., 2012). Similarly, cultural differences in sleep deserve further attention. For example, for some families, co-sleeping occurs in response to sleep problems, whereas for some families it is a culturally appropriate practice (Owens, 2004). Finally, including psychiatric control groups in sleep studies would be beneficial. Many studies use either TD children or those with other DDs as controls. However, high rates of comorbidity (e.g., anxiety, attention impairments) suggest that psychiatric comparison groups would be valuable in advancing our understanding of the nature and effects of sleep disturbance.

Most of what we know about sleep disturbance in NDDs comes from caregiver report, which can provide valuable information about children's sleep, is cost-effective, and easier to collect from large samples. However, overreliance on caregiver report alone can be problematic. To address the difficulty of obtaining objective measures of sleep, some groups have modified actigraphy by placing equipment in a shirt pocket or sock (e.g., Moss et al., 2014). Others have used portable PSG in the home (Breslin et al., 2014). Caregivers can implement behavioral interventions and use social stories to desensitize children to wearing equipment (e.g., Moore, Evans, Hanvey, & Johnson, 2017). Videosomnography, a less commonly used method, can provide objective data on some aspects of children's sleep without requiring them to wear equipment (Moore et al., 2017).

Much remains to be learned about sleep disturbance in NDDs. The research landscape is full of possibilities. We have strived to summarize the literature, to identify existing knowledge gaps, and to offer suggestions for further investigation. This review demonstrates the importance of understanding sleep disturbance and improving sleep for children with NDDs. An early focus on sleep may help to prevent or alleviate at least some symptoms associated with different NDDs, and improve quality of life for children and families. Deepening our understanding of sleep disturbance in NDDs may also serve to advance our understanding of etiology and development of effective treatments.

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