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Review

Circadian rhythms and sleep in children with autism

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ABSTRACT

A growing body of research has identified significant sleep problems in children with autism. Disturbed sleep–wake patterns and abnormal hormone profiles in children with autism suggest an underlying impairment of the circadian timing system. Reviewing normal and dysfunctional relationships between sleep and circadian rhythms will enable comparisons to sleep problems in children with autism, prompt a reexamination of existing literature and offer suggestions for future inquiry. In addition, sleep and circadian rhythms continue to change over the course of development even in typical, healthy humans. Therefore, exploring the dynamic relationship between circadian rhythms and sleep throughout development provides valuable insight into those sleep problems associated with autism. Ultimately, a better understanding of sleep and circadian rhythms in children with autism may help guide appropriate treatment strategies and minimize the negative impact of these disturbances on both the children and their families.

Contents

1. Introduction

Many children with autism suffer some form of sleep disturbance (Richdale, 1999). Although the consequences of sleep problems have been more extensively studied in adults, sleep loss in children and adolescents has been associated with daytime sleepiness and impaired performance at school (Meijer et al., 2000; Wolfson and Carskadon, 2005). Furthermore, parents of children with autism report their own sleep is disrupted as a result of their child's sleeping patterns (Polemini et al., 2005). Negative consequences of sleep disturbance could therefore also threaten the efficacy of behavioral treatments for children with autism, both in terms of performance of the child as well as the ability of the parents to properly employ learned treatment strategies and techniques.

Increased sleep latencies, waking during the night and difficulty awakening in the morning are among the most frequently reported problems (Patzold et al., 1998; Richdale and Prior, 1995; Wiggs and Stores, 2004; Williams et al., 2004), resulting in less overall total sleep. Such abnormalities suggest that the sleep problems may represent a circadian disturbance in the daily timing of neurobehavioral and endocrine functions. This theory is supported by limited information regarding abnormal cortisol and melatonin

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profiles in children with autism (Corbett et al., 2006, 2008; Curin et al., 2003; Kulman et al., 2000; Richdale and Prior, 1992; Ritvo et al., 1993; Tordjman et al., 1997, 2005). Although recent efficacy studies of melatonin treatment to correct sleep in these children are based on impairment of the circadian system (Andersen et al., 2008; Paavonen et al., 2003), few published reports have thoroughly examined the putative association between sleep disturbance and circadian rhythms in autism (Richdale, 1999). Furthermore, sleep and hormonal patterns in autism have not been examined within the context of normal development of circadian rhythms nor have current models of sleep been applied as a framework for considering the most common sleep problems in these children. The goal of this paper is to characterize what is currently known about sleep and circadian rhythms as a way to gain insight into the sleep disturbance often reported in children with autism.

2. Sleep and circadian rhythms

A well recognized model of sleep posits that there are two principle modulators of sleep and wakefulness: sleep homeostasis and the circadian pacemaker (Borbély, 1982; Borbély et al., 1989; see Fig. 1). Under normal conditions, relative coordination of the sleep homeostatic and circadian systems is what accounts for a typical daily schedule in adults, with 16 h of constant wakefulness during the day and 8 h of consolidated sleep at night (Dijk and Czeisler, 1995).

Sleep homeostasis is a regulatory mechanism based on prior duration of continuous sleep and wakefulness. Homeostatic pressure to initiate and maintain sleep gradually accumulates as the duration of wakefulness increases and diminishes over the course of a sleep episode. The level of slow-wave activity (SWA) in the initial part of sleep is determined by prior durations of sleep and waking, and has therefore been utilized as an indicator of homeostatic sleep regulation (Achermann and Borbély, 1997). SWA is a particularly good marker since it is relatively unaffected by the circadian system (Achermann and Borbély, 1997; Dijk et al., 1987).

The circadian aspect of sleep, on the other hand, is largely independent of sleep history. Instead, the circadian system represents the action of an endogenous biological clock, or pacemaker, located in the suprachiasmatic nucleus (SCN) of the hypothalamus. Circadian rhythms are physiological and behavioral processes that have an internally generated cycle with a period of approximately 24 h. The human circadian period is normally slightly longer than 24 h (Czeisler et al., 1999). In addition to the sleep–wake cycle, there are various other biological functions that demonstrate circadian properties, including core body temperature fluctuations and certain hormone secretory patterns. These endogenous rhythms may be reset daily to 24-h cycles in the environment via *zeitgebers*, with the most important signal being the natural light–dark cycle, although other cues may also be relevant. For example, non-photic signals such as sound, social cues and conditioning have all been found to influence endogenous rhythms (Amir and Stewart, 1996; Aschoff, 1981; Mrosovsky, 1996).

Normally, human circadian rhythms are synchronized or entrained to a 24-h period via daily light-induced phase shifts that adjust the endogenous period to match the period of the environmental light–dark cycle. These shifts are indicative of differential effects of light on the SCN at different phases (Moore, 1983; Klein et al., 1991). During entrainment, the different outputs maintain a stable temporal relationship to one another (see Fig. 2). It is noteworthy that overt rhythms may be altered by the state of the pacemaker or a "masking effect" may occur wherein the measured output is affected without disrupting the pacemaker itself. Being able to distinguish between a disrupted clock and a masking response in human experiments is best accomplished via the study of multiple outputs within the same individual.

3. Circadian sleep disorders

Normal patterns of sleep and circadian rhythms may become disrupted as a result of a misalignment between the circadian system and the sleep–wake cycle or via direct impairment of circadian functioning. A hallmark characteristic of most circadian sleep disorders is the inability to sleep during desired times, with common complaints of difficulty in initiating or maintaining sleep, early awakening and/or impaired alertness during waking hours. Interestingly, these are also among the most common sleep problems found in children with autism (Patzold et al., 1998; Richdale and Prior, 1995; Wiggs and Stores, 2004; Williams et al., 2004) and in those with associated conditions, such as Smith–Magenis Syndrome (Smith et al., 1998), Rett Syndrome (Sekul and Percy, 1992) and Angelman Syndrome (Bruni et al., 2004). Examining some of the known circadian disorders will be helpful in better understanding the sleep disturbance in children with autism as well as in developing recommendations for future study and treatment.

According to the second edition of the International Classification of Sleep Disorders (ICSD-2) (2005), there are six primary circadian rhythm sleep disorders: *delayed sleep-phase syndrome* (*DSPS*), *advanced sleep-phase syndrome* (*ASPS*), *free-running type*, *irregular sleep–wake type, shift work sleep disorder*, *and jet lag*. All have specific diagnostic criteria, which will not be detailed here. However, the characteristic patterns of sleep and circadian

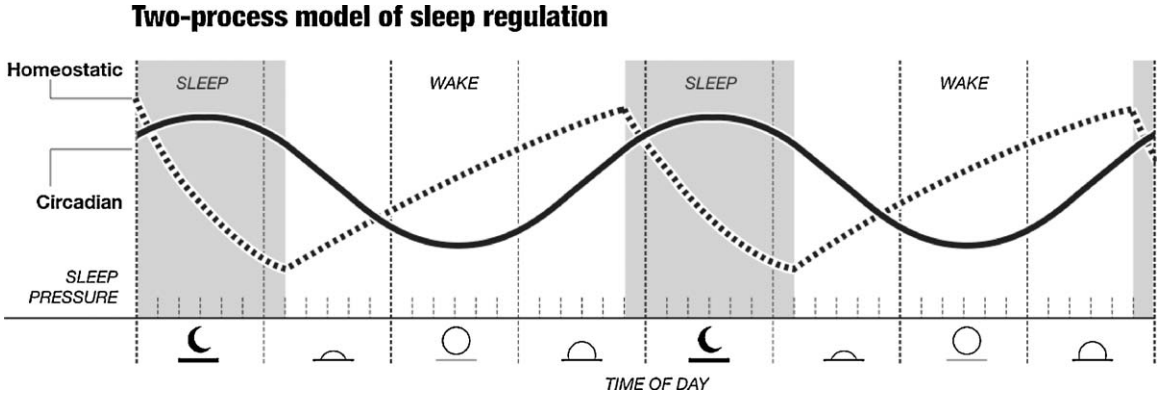

Fig. 1. This illustration describes the two-process model of sleep regulation, including circadian and homeostatic components. Schematic modified from Achermann and Borbély (2003).

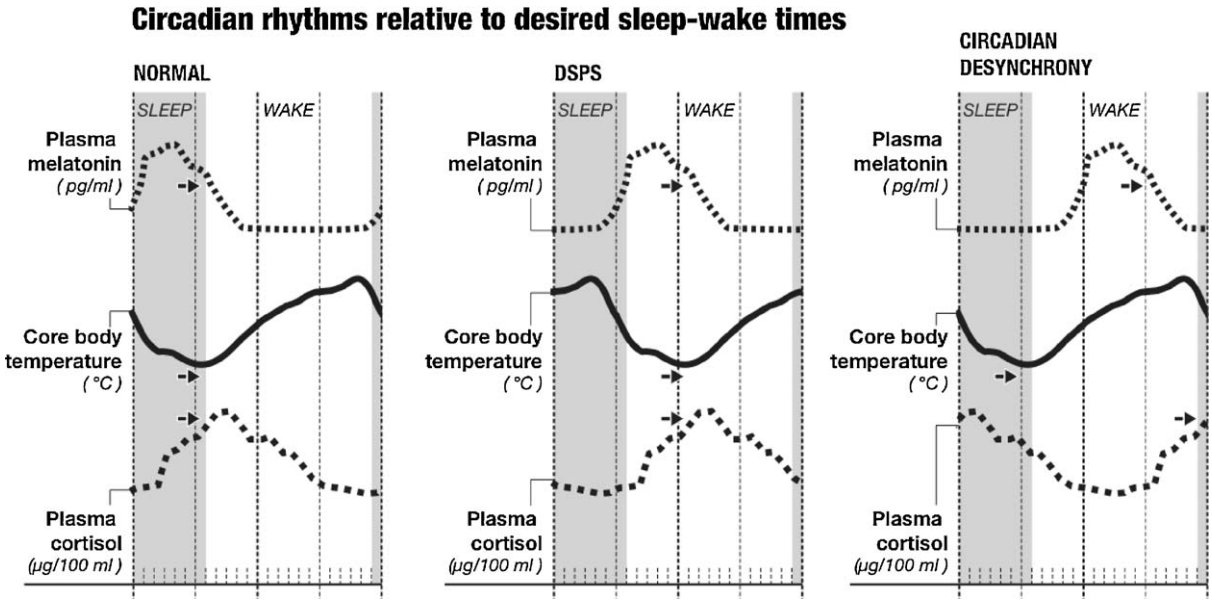

Fig. 2. The graphs above represent theoretical relationships between circadian rhythms in melatonin, core body temperature and cortisol within the context of desired sleep (areas in shaded grey) and wake (areas in white) times. Normal conditions are illustrated in the first column, wherein different circadian outputs are synchronized to a 24-h environmental light–dark cycle and maintain a stable temporal relationship to one another. In Delayed Sleep-Phase Syndrome (DSPS; middle column), the circadian phase of rhythms are each similarly delayed relative to desired sleep–wake times. Finally, desynchronous conditions may occur when circadian rhythms are misaligned due to imposed alterations in light–dark cycles and sleep–wake times.

rhythms in each of these are very different and will therefore be summarized, along with a brief description of some of the proposed causes. Generally, circadian sleep disorders likely represent impairments in the generation of circadian rhythms and/or circadian entrainment processes.

DSPS and *ASPS* are both chronic disorders in the timing of sleep relative to standard prescribed schedules. Importantly, all other circadian rhythms are shifted in a corresponding manner (see Fig. 2). For example, *DSPS* is marked by a relative delayed circadian phase, with later sleep onset and wake times as well as equivalent delays in core body temperature and melatonin rhythms (Oren et al., 1995; Ozaki et al., 1988; Wyatt et al., 2006). Individuals with *ASPS* also have sleep and circadian rhythms that are displaced relative to desired sleep times; however in this case, rhythms are instead shifted to an earlier time than what is dictated by societal norms (Jones et al., 1999; Satoh et al., 2003). In both instances, the biological clock is consistently out of phase with environmental cues, but there would not be a sleep problem per se if individuals were allowed to follow their own schedules. It is only within the context of conventional schedules, based on the 24-h natural light–dark cycle, that these behaviors become dysfunctional. It has been suggested that *DSPS* and *ASPS* may be a consequence of abnormal periods of the intrinsic circadian rhythm (i.e. extremely lengthened period in *DSPS*/shorted period for *ASPS*) and/or impairment in the ability to entrain to available environmental time cues (Aoki et al., 2001; Jones et al., 1999; Wyatt et al., 2006). Unlike the other circadian disorders, an underlying genetic component has been identified in ASPS and DSPS as both disorders have been found to run in families (Ancoli-Israel et al., 2001; Jones et al., 1999). More recent work specifically implicates the human Per and casein kinase Iδ (CKIδ) genes in the familial variants of DSPS and ASPS (Archer et al., 2003; Ebisawa et al., 2001; Nadkarni et al., 2005; Toh et al., 2001; Xu et al., 2005).

Free-running rhythm sleep disorder, as the name suggests, is a condition in which a patient's circadian functions follow their own individual endogenous clock period. Such a rhythm is similar to those of healthy subjects maintained under constant conditions, in the absence of temporal cues (Czeisler et al., 1999). This disorder is also most often observed in blind patients (Sack et al., 1992). Consequently, free-running rhythm disorder is thought to be due to a dysfunction in photic entrainment mechanisms.

Diagnosis of *irregular sleep wake* type is used to describe an individual who has a sleep–wake pattern completely lacking a circadian rhythm. Those with this disorder may get a relatively normal total amount of sleep, however it is in the form of multiple short episodes of sleep randomly distributed throughout the day and night. This type of sleep disturbance is most often found in individuals with neurological impairments, such as children with mental retardation, individuals with head injuries and older adults with Alzheimer's disease (Hoogendijk et al., 1996; Witting et al., 1990). Although the underlying cause remains unknown, the integrity of the SCN is likely compromised as these sleep patterns mimic the activity rhythms of animals with SCN lesions (Stephan and Zucker, 1972). A polyphasic pattern of sleep is also found in infants prior to maturation of the circadian system, though total sleep time is significantly increased in infants as well (Anders et al., 1995).

Healthy individuals generally maintain a 24-h period that closely matches environmental cycles; however, even their circadian rhythms can become misaligned. The extended absence of temporal cues or a dramatic shift in the relationship between sleep and environmental cycles can pose a significant challenge to the circadian system. In both instances, sleep–wake patterns begin to deviate from the 24-h rhythm and become desynchronized relative to other circadian functions (Kronauer et al., 1982). Common causes of this condition include intercontinental travel across multiple time zones and shift work schedules. While *jet lag* tends to be a temporary state, *shift work sleep disorder* is often chronic. Problems frequently associated with shift work include reduced alertness at work and impaired sleep quality (Czeisler et al., 1990; Eastman, 1990; Moore-Ede et al., 1983). In addition, shift work has been associated with a variety of negative health consequences that are thought to be at least partly due to repeated desynchronization of the circadian system, including cardiovascular disease, gastrointestinal disorders and cognitive as well as psychological disturbances (Czeisler et al., 1990; Eastman, 1990; Eastman et al., 1995; Moore-Ede et al., 1983).

Circadian sleep problems have been studied rather extensively in adults. Currently, the most common treatments include

pharmacological administration of melatonin (Dahlitz et al., 1991; Herxheimer and Petrie, 2002; Lockley et al., 2000; Sack et al., 1991), light therapy (Boulos et al., 2002; Eastman, 1990; Eastman et al., 1995; Lack et al., 2005; Rosenthal et al., 1990; Samel and Wegmann, 1997), and promotion of lifestyles that allow for individual preferred sleep–wake times. In the following sections, these established circadian sleep disorders are used as templates for interpreting the most common sleep problems in children with autism. Referring to circadian sleep disorders will help to identify potential underlying causes, negative consequences and treatments that should be considered in children with autism. Likewise, further knowledge of those sleep problems in children with autism may inform our understanding of the relationship between sleep and circadian rhythms.

4. Sleep and circadian rhythms in children with autism

Some have conjectured that the frequently reported sleep problems in children with autism may be due to a circadian disturbance (Patzold et al., 1998; Richdale and Prior, 1995). Yet published reports examining the putative relationship between sleep disturbance and circadian rhythms in children with autism have been limited (Richdale, 1999). A current review of the literature is timely due to a subsequent surge in studies confirming and refining those earlier insights. Still, speculation of circadian impairment is based largely on two separate bodies of knowledge. An extensive and relatively consistent literature identifies the presence of sleep disturbances in children with autism and to a somewhat lesser extent, characterizes those problems. In contrast, studies investigating circadian regulation in children with autism are far more limited, and findings are marked by less agreement. Few studies have examined both sleep and circadian rhythm changes in children with autism in the same group of subjects. This section will outline and discuss relevant research, propose novel ways of considering existing data and highlight some of the challenges in interpreting the present collection of studies.

High rates of sleep problems in children with Autism Spectrum Disorders (ASDs) have been reported over the past three decades (DeMeyer, 1979; Hoshino et al., 1984; Patzold et al., 1998; Taira et al., 1998; Wiggs and Stores, 2004), and the number and quality of such studies has increased significantly in recent years. A large study based on parental report estimates prevalence of sleep problems to be approximately 44–83% in children with autism (Richdale and Prior, 1995). In contrast, only 20–30% of typically developing infants and preschool children present with sleep problems (Beltrami and Hertzig, 1983; Owens et al., 2000). When examining older, school-age children, these numbers become significantly reduced to 10.8% (Stein et al., 2001). Not only do autistic children consistently demonstrate a higher rate of sleep disturbance than typically developing children, but prevalence is even higher than that seen in children with other developmental disorders (Cotton and Richdale, 2006; Owens et al., 2000) despite the fact that sleep problems are more frequently observed in intellectually handicapped children, in general (see Stores, 1992, for review).

Sleep disturbances found in autistic children do not appear to be artifacts of co-morbidity with intellectual dysfunction. Firstly, intelligence quotient (IQ) is not inversely related to sleep impairment in autism, as it is with most developmental disabilities (Patzold et al., 1998; Richdale and Prior, 1995; Stores, 1992). On the contrary, it is children with higher IQs who actually show relative decreased overall reported sleep times, with longer sleep latencies and longer periods awake during the night (Richdale and Prior, 1995). Younger children with higher intellectual functioning also demonstrate earlier wake times (Richdale and Prior, 1995). Further evidence that the sleep problems are not solely a product of intellectual impairment comes from a study showing reduced total sleep times and increased sleep latencies in children with autism as compared to age-, gender- and IQ-matched controls (Patzold et al., 1998). Moreover, sleep problems do not correlate with IQ in those children (Patzold et al., 1998).

While that earlier work was primarily based on subjective parental report and sleep diaries, several more current studies employing objective actigraphy and polysomnography measures generally confirm prior findings and demonstrate the ability to use this equipment in children with autism (Allik et al., 2006; Daoust et al., 2004; Diomedi et al., 1999; Elia et al., 2000; Limoges et al., 2005; Øyane and Bjorvatn, 2005; Thirumalai et al., 2002; Wiggs and Stores, 2004). Actigraphs measure activity patterns via wristwatch-like devices that contain miniature accelerometers, and at least 5 nights of monitoring are recommended in order to accurately assess sleep patterns in children (Acebo et al., 1999). The first study to employ actigraphy did not find many significant differences in sleep between children with autism and typical controls, despite parental report of increased sleep problems in the autism group (Hering et al., 1999). Statistical differences were found only in morning waking times. That study, however, collected data for a limited amount of time (72 h) in a small group of children with autism ($n = 8$), and the authors reported difficulty utilizing the actigraph device in a relatively large number of autistic children with reported sleep problems. Those children were consequently not included in the study and therefore, children who were included in the group may have also represented children with more mild sleep problems (Hering et al., 1999). Consistent with this possibility, children with increased sleep problems tend to have more daytime behavior problems (Hoffman et al., 2005; Liu et al., 2006; Malow et al., 2006; Schreck et al., 2004).

More recent actigraphy studies have determined that children with autism have significant sleep problems (Allik et al., 2006; Øyane and Bjorvatn, 2005; Wiggs and Stores, 2004). The study by Wiggs and Stores (2004) represents the most extensive study of its kind to date. The sleep patterns of 69 children with ASDs were monitored over 5 days, and sleep disturbances were found even when problems were not identified by parental report. Long sleep latencies, delayed or advanced sleep onset and offset, and nighttime waking were among the most frequently found sleep problems, consistent with previous diary and questionnaire reports (Wiggs and Stores, 2004). These types of sleep deficits resemble many of the symptoms of the various aforementioned circadian sleep disorders (ICSD-2, 2005). Additional common reports of decreased total sleep times and subjective sleepiness are less specific indicators of sleep problems, but may also underscore circadian sleep disturbance.

Wiggs and Stores (2004) were, in fact, the first to carefully characterize observed sleep problems according to standardized diagnostic criteria. The challenge of such categorization is illustrated by the necessity of an "Other" category, which was created for a large minority of children for which sleep problems did not precisely meet standard classification. Due to some of the idiosyncrasies of autism and children in general, conventional characterizations may result in misleading conclusions and recommendations. In their study, eight children were determined to have circadian sleep–wake problems, and 36 of the children had behavioral sleep problems. Although circadian sleep disorders were well represented, circadian disturbance may have actually been under-estimated.

Behavioral sleep problems, including limit setting sleep disorder and sleep onset association disorder, were reported in more than 50% of the children (Wiggs and Stores, 2004). Limit setting problems were the more common of the two behavioral problems and were defined by the following: difficulty initiating

and falling asleep, stalling/refusing to go to bed, and normal sleep quality and quantity once asleep. This description bears a resemblance to DSPS, which is also marked by difficulty falling asleep (ICSD-2, 2005). While DSPS does not include reference to "stalling" or "refusal" to go to bed, a diagnosis historically made in otherwise healthy adults would not likely include the use of such terms in describing the sleep time restlessness that is typical. Individuals with DSPS also do not always demonstrate normal sleep quantity once asleep, but this is due to the fact that sleep is curtailed by imposed schedules. Because this study included children within a wide age range (i.e. 5–16 years old) in a variety of educational settings, morning wake time demands may have varied between subjects (Wiggs and Stores, 2004). This possibility is supported by the fact that sleep problems labeled as behavioral were found more frequently in the youngest children. In the event that these younger children were allowed to wake up later in the morning and thereby get a normal amount of sleep, the possibility that they possess a phase delay of their circadian rhythms should not be excluded. The combination of symptoms described may also reflect a homeostatic disturbance wherein sleep propensity accumulates too slowly in these children. Due to some of the challenges described, it is important to carefully examine sleep patterns within the context of social demands. Furthermore, examining sleep patterns alone will not likely provide conclusive information regarding underlying cause.

The less common of the two behavioral problems identified in this large-scale study, sleep onset association disorder, was defined by: complaint of sleeplessness, sleeplessness associated with the absence of certain conditions (examples given included parental presence and television viewing), normal sleep quality and quantity when the associations were present, and increased sleeplessness when the associations were absent (Wiggs and Stores, 2004). While such characteristics may be viewed as a behavioral problem, those conditions and associations important for normal sleep in some children could be serving as entraining cues. Social cues, to which children with autism may be less attuned, may be an important zeitgeber in humans (Aschoff et al., 1971; Klerman et al., 1998). Therefore, these children may be relying on other signals in their environment to obtain time of day information. Although the predicted consequences would be inconsistent with this particular categorization, the report of conditions such as watching television and parental presence indicates the allowance of behaviors that can negatively impact sleep and circadian physiology. In fact, such behaviors were not controlled for nor reported in most of the aforementioned outpatient sleep studies. For example, environmental factors, such as keeping the bedroom dark and free of arousing stimuli are important aspects of good sleep hygiene that were typically not addressed. In addition, the time some children are put to bed may be slightly too early, coinciding with the period of strongest circadian-driven alerting and therefore, interfering with the initiation of the sleep episode (see Fig. 1). Though examining naturalistic behaviors is important for initial assessments, imposing additional control over such factors will enable refinement in the characterization of sleep problems and potentially, effectively treat certain children without the need for further intervention.

Finally, while actigraphy represents progress in terms of utilizing more objective measures of sleep patterns, polysomnography has also been employed as a means for examining sleep architecture more closely under relatively more controlled conditions. Polysomnography (PSG) studies have identified a variety of sleep difficulties in children with ASDs, including the following features: longer sleep latencies, frequent night waking, lower sleep efficiency (i.e. sleep as a percentage of time in bed), decreased non-REM and SWA sleep, lower sleep spindle density, REM sleep abnormalities, periodic limb movements in sleep, and decreased sleep in the first two thirds of the night (Daoust et al., 2004; Diomedi et al., 1999; Elia et al., 2000; Limoges et al., 2005; Malow et al., 2006; Thirumalai et al., 2002). These studies have examined smaller samples and the demographic varies across studies in terms of both age and level of intellectual functioning, yet findings are reasonably consistent with subjective reports and actigraphy data. For example, in their study of males 5–16 years old, Elia et al. (2000) found that those with autism ($n = 17$) spent significantly less time asleep in comparison to controls, with total sleep times of 7 h 30 min and 8 h 43 min, respectively. Another study of individuals with autism aged 12–24 years reported relatively less efficient sleep, with a higher incidence of nighttime waking in autistic individuals (mean of 11.4 awakenings in the autism group versus 4.2 among controls) (Diomedi et al., 1999). Although control subjects were matched for age and sex, autistic subjects in this study were also mentally retarded, with significantly lower IQs (Diomedi et al., 1999). A more recent study characterized sleep in 21 children 4–10 years of age with ASD, employing stringent inclusion factors wherein patients were required to be without mental retardation or seizure disorder and medication-free (Malow et al., 2006). Still, decreased sleep efficiency and increased sleep latencies were found in those children identified as "poor sleepers" via parental report (Malow et al., 2006). An important aspect of this study was the inclusion of a comparison group of children with ASD reported by their parents to be "good sleepers." Their normal sleep quality was confirmed via PSG, calling attention to the important fact that not all children with autism suffer sleep disturbance as well as the potential value of parental report in assessing sleep problems in children (Malow et al., 2006). There is also indication of impairment to homeostatic sleep functions, as reduced SWA in the earlier portion of the sleep episode has been observed in adolescents and young adults (16–27 years old) with autism (Limoges et al., 2005).

In summary, sleep assessments have ranged from subjective report to laboratory studies with varied levels of control over relevant factors, yet there is now a compelling body of literature identifying increased sleep problems in children with autism. The aforementioned work primarily aimed to determine prevalence and describe sleep problems. Delayed sleep onset, waking during the night and early morning waking have been those most commonly reported across studies and implicate involvement of the circadian system (Diomedi et al., 1999; Elia et al., 2000; Patzold et al., 1998; Richdale and Prior, 1995; Wiggs and Stores, 2004). Although irregular sleep patterns that appear to have circadian origins are merely a fraction of all reported problems (Wiggs and Stores, 2004), this subset may represent a relatively larger proportion than has been previously considered. Studies thus far represent an important first step in determining the range and frequency of the different sleep disturbances encountered by children with autism. Future research should now focus more on particular types of sleep problems. Not only does ASD represent a broad spectrum of disability (Walker et al., 2004) but "sleep problems" is patently generic. Failure to distinguish between different types of sleep problems via actigraphy and/or polysomnography could lead to a diluting of any differences that might be observed with more careful characterization. Conditions co-morbid to autism that can affect sleep, such as seizure disorder and depression, can also complicate the interpretation of results and must be considered. Identifying unique patterns of sleep inherent to children with specific co-morbidities may be particularly useful for prognosis and treatment. Finally, examining other overt rhythms in children with autism and probable circadian disturbances will be important to better understanding the underlying physiology associated with these more common sleep problems.

5. Relationship of melatonin to sleep and circadian rhythms

One of the best markers of the human circadian pacemaker is the pineal hormone melatonin rhythm. The natural light–dark cycle entrains the rhythmic synthesis and secretion of melatonin via a neural pathway separate from the visual system, called the retinohypothalamic tract (RHT) (Klein et al., 1991; Moore, 1983). In all species, including humans, melatonin secretion is high at night and low during the day (Arendt, 1995; Tamarkin et al., 1980). Specifically, in individuals normally entrained to the environmental light–dark cycle, melatonin levels begin to rise in the evening (8:00–11:00 PM), peak in the early morning hours (2:00–4:00 AM) and return to baseline at ~8:00–10:00 AM (see Fig. 2). Due to significant individual variability in raw melatonin levels, measurement at a single time point is not sufficient to provide a meaningful melatonin profile, and it is therefore important to regularly collect samples across at least one complete 24-h period (Burgess and Fogg, 2008). Melatonin profiles can be an extremely robust indicator of phase because this hormone is unaffected by most external factors, except for light. In addition to entraining the circadian melatonin rhythm, light exposure at night can acutely disrupt activity of the pineal enzyme serotonin-N acetyltransferase and consequently, elicit a marked depression in circulating melatonin levels. The acute light-induced suppression of melatonin has been well established in humans (Brainard et al., 2001; Glickman et al., 2003; Lewy et al., 1980). Melatonin has also been used both to characterize (Jones et al., 1999; Oren et al., 1995) and treat circadian sleep disorders (Dahlitz et al., 1991; Herxheimer and Petrie, 2002; Lockley et al., 2000; Sack et al., 1991).

Sleep behaviors appear to be strongly linked to melatonin in humans. Melatonin onset typically occurs approximately 2 h prior to the evening rise in sleep propensity (Schochat et al., 1998; Tzischinsky et al., 1993). In addition, impairments in sleep consolidation correspond to the circadian phase when melatonin secretion is low and improve when sleep times coincide with relatively higher melatonin levels (Dijk et al., 1995a,b). It has been suggested that melatonin may play an active role in suppressing the circadian signal promoting wakefulness in humans (Lavie, 1997; Sack and Lewy, 1997). This notion is supported by observations of sleep after administration of exogenous melatonin wherein low doses lead to rapid increases in sleep propensity, sleep consolidation and subjective sleepiness as well as decreased latencies to stages 1 and 2 sleep (Dollins et al., 1994; Hughes et al., 1994; Reid et al., 1996; Roach et al., 2006; Schochat et al., 1998; Tzischinsky et al., 1993; Tzischinsky and Lavie, 1994; Van den Heuvel et al., 1998). Since melatonin is also high during the night in nocturnal species (Tamarkin et al., 1980), a time when these animals are active rather than asleep, the hormone does not serve to directly promote sleep. Instead, melatonin may more accurately be described as a signal of subjective night (Lewy et al., 1999), which is the appropriate time for sleep in humans. Still, when taken together, the above studies indicate that melatonin is not only a useful marker of circadian phase, but may also influence sleep in humans. Consequently, there is high utility in examining melatonin profiles in order to further understand circadian rhythms and sleep in children with autism.

6. Hormone profiles in children with autism

Neuroendocrine markers provide additional circadian endpoints that are less subject to social influences. Both cortisol and melatonin levels have been quantified in children with autism via sampling of blood, urine and saliva. Known studies of hormones and autism will be described in order to assess what are likely to be the most reliable findings. Better understanding of these overt rhythms in children with autism will provide an important clue in determining the circadian contribution to the sleep disturbance that is common in this population.

Cortisol is a corticosteroid hormone found in humans that exhibits diurnal variations, beginning in early infancy (see Table 1; Antonini et al., 2000; Mantagos et al., 1998). Cortisol rhythms are normally displaced relative to melatonin fluctuations, as cortisol levels peak in the morning just after waking, decrease rapidly over the course of the morning, and decline more slowly later in the afternoon to the lowest levels in the evening (see Fig. 2). Studies of cortisol rhythms in children with autism are somewhat inconclusive (Corbett et al., 2006, 2008; Curin et al., 2003; Hill et al., 1977; Hoshino et al., 1987; Richdale and Prior, 1992; Tordjman et al., 1997), and findings may be influenced by the hormone's potentially confounding role in stress response (Corbett et al., 2006; Kirschbaum and Hellhammer, 1994). In order to minimize a potential masking by stress, most of the labs studying cortisol have chosen to employ saliva (Corbett et al., 2006, 2008; Hoshino et al., 1987) or urine collection (Richdale and Prior, 1992) as opposed to blood (Curin et al., 2003; Hill et al., 1977). Outpatient studies in the child's home serve to further minimize stress by avoiding the need to be in a foreign environment, although control over study parameters may be compromised as well, such as the timing of sample collection.

While recognizing that the studies examining cortisol in blood may be more confounded by the stress of such collection methods, they each have their own respective strengths (Curin et al., 2003; Hill et al., 1977; Nir, 1995). An earlier experiment, albeit small in sample size, was one of the only studies found that measured multiple overt rhythms in children with autism (Hill et al., 1977). Specifically, plasma cortisol and core body temperature were each measured every 4 h over the course of a 24-h period in 6 children with autism (5–9 years of age). Although the control group was not age-matched and included only 3 typical children aged 9–11 years old, results included: a relative earlier rise, lower daytime levels and multiple peaks in cortisol in the children with autism. Within the autism group, only one child showed the expected early morning drop in temperature preceding the morning cortisol peak, and all others lacked a clear temperature rhythm (Hill et al., 1977). Monitoring core body temperature is a relatively invasive procedure that children are unlikely to tolerate well, even though that study did not report any difficulties in obtaining temperature data. Multiple rhythms, including both cortisol and melatonin, were examined in relatively older subjects aged 16–23 (Nir, 1995). While that study also had a rather small sample size ($n = 10$), no significant differences in cortisol were found. Differences in melatonin profiles were reported and will be discussed later (Nir, 1995). The third study that collected blood examined serum levels in a much larger sample size of autistic children ($n = 36$) at one morning time point between 8:00 and 9:00 AM (Curin et al., 2003). Decreased levels were found in children with autism relative to controls. The control group was matched by age but not in terms of IQ; however, the authors were able to divide autistic subjects into three IQ ranges. Analysis of these groups found that mean cortisol levels were not significantly different as a function of IQ, and all were statistically lower than the control group. The lowered morning cortisol level might indicate a dampened amplitude, displaced rhythm, or even discrepant stress response, independent of IQ. Unfortunately, assessment at one time point cannot further clarify the nature of any potential abnormalities (Curin et al., 2003).

Changes across subsequent days and increased individual variability of cortisol rhythms in children with autism have also been found (Corbett et al., 2006; Richdale and Prior, 1992). Richdale and Prior (1992) studied high-functioning autistic children with IQs ranging from 58 to 112 as compared to age-, sex- and IQ-matched controls. Urine samples were collected by

Table 1
Development of sleep and circadian rhythms.

Age	Circadian	Sleep
Fetus	– SCN formation (Reppert et al., 1988) and SCN innervation by the retinohypothalamic tract (RHT) are both completed by mid-gestation (Glotzbach et al., 1992; Hao and Rivkees, 1999) – Melatonin receptors are found in the SCN and other areas of the brain (Thomas et al., 2002) – Melatonin rhythms are present in fetal circulation from the mother's rhythms (Yellon and Longo, 1988) – Diurnal fluctuations are observed in measures of activity, breathing and heart rate (Seron-Ferre et al., 2001a, for review)	– During gestation, 90–95% of the day is spent sleeping (Curzi-Dascalova et al., 2008)
0–1 months	– Body temperature rhythms are observed during the first days of life in pre-term infants, even in the absence of temporal cues (Mirmiran and Ariagno, 2000)	– Polyphasic pattern of sleep, marked by multiple sleep bouts of ∼4 h each totaling ∼16–17 h in the newborn (Parmelee et al., 1964; Anders et al., 1995) – Gradual lengthening of both nighttime sleep period and daytime wakefulness (Coons and Guilleminault, 1984)
2–3 months	– Circadian rhythms of melatonin production and secretion emerge (Kennaway et al., 1992, 1996; Ardura et al., 2003) – Cortisol rhythms appear (Mantagos et al., 1998; Antonini et al., 2000) – Entrainment of sleep–wake rhythms to light–dark cycles is observed in most infants (Shimada et al., 1999)	– Day–night rhythms in activity emerge (Coons and Guilleminault, 1984) – Longer nighttime sleep episode, with two daytime naps (Parmelee et al., 1964) – Reduced total sleep time of 15 h (Parmelee et al., 1964) – Higher level of SWA earlier versus later in the night (Bes et al., 1991)
3–6 months		– Gradual decline in awakenings during the night (Scher, 1991) – By 6 months, a consolidated period of sleep longer than 6 h occurs during the night and total sleep duration averages ∼14.2 h (Iglowstein et al., 2003)
9 months		– Increased nighttime waking (Anders et al., 1992; Scher, 1991)
12 months		– Infants gradually reduce to one nap per day and 13.9 h total by the end of their first year (Iglowstein et al., 2003)
2 years		– Regular night waking becomes significantly less common (Sadeh et al., 1991) – Total sleep time is further reduced to ∼13.2 h (Iglowstein et al., 2003)
4–10 years		– The daytime nap is no longer needed, and children have one ∼11 h nighttime sleep episode (Iglowstein et al., 2003)
11 years		– Typically, older children have one ∼9 h nighttime sleep episode (Iglowstein et al., 2003)

This table summarizes landmark events during early human development of sleep and circadian systems, including both behavioral and biological factors.

parents in the home approximately every 2 h on two different weekend days, each separated by a week. Parents were instructed to obtain samples starting with the first following sleep onset and every 2 h thereafter until bedtime, without continuous nighttime sampling. Sleep information was collected via diaries that were kept for 14 days in the previous month as well as on the days of urine sample collection. Urination times were adjusted relative to overall mean wake time during those previous 2 weeks, as an important aspect of managing circadian data is accounting for individual differences in circadian phase. There is, however, reason to believe that the 14 day period was not representative of wake times on the weekend as it was reported that more than 20% of the children slept relatively later on at least one of the two days of sampling. Independent of the fact that sleeping in on weekends is consistent with DSPS, discrete weekend days may not be typical of weekly sleep patterns and/or hormone rhythms. Nevertheless, mean cortisol levels trended higher in children with autism at all time points (Richdale and Prior, 1992). In the first weekend samples, it was the first three samples that showed consistently higher values in children with autism whereas in the second weekend, the later samples trended higher than controls, demonstrating changes over the course of the week. Lack of continuous data in between the two weekends does not allow for further understanding of this trend but does suggest a possible dysfunction in entrainment, as the cortisol rhythm appears to be drifting later relative to environmental clock time, particularly in the older children with autism (Richdale and Prior, 1992). This drifting in peak cortisol secretion in older autistic subjects was also noted by the authors as the possible reason for lack of statistically significant differences in mean peak time levels, despite the trend for increased cortisol in autistic subjects. Habituation to the procedures may also be delaying increases in cortisol in the older children but not younger children, reflecting a differential stress response. Finally, it was reported that 39% of the children with autism actually showed cortisol values that were equivalent or higher than relatively earlier levels, deviating from the mean pattern of peaking in the morning. Sleep patterns on days of sample collection were not reported in conjunction with the cortisol data (Richdale and Prior, 1992).

Studies from Corbett and colleagues were the first to regularly examine cortisol levels continuously over a matter of days in autistic children and age-matched control subjects (Corbett et al., 2006, 2008). In their latter expanded study, three salivary samples were collected each day (morning, afternoon and evening) for 6 days total (Corbett et al., 2008). They found a gradual decrease over time in the peak morning values, an increase in evening values and greater within-subject variability in cortisol levels for the autism group (Corbett et al., 2006, 2008). While those results suggest some abnormality of daily cortisol fluctuations in autistic subjects, lack of resolution of this circadian rhythm makes it difficult to determine whether this represents a reduced amplitude over time or a shifting of individual rhythms.

The aforementioned data suggest abnormal cortisol profiles in children with autism in all but one study (Nir, 1995). The greater

variability of cortisol values in children with autism not only suggests circadian disturbances, but emphasizes the caution that must be taken when interpreting results of studies with smaller sample sizes (Corbett et al., 2006, 2008). Studies that included multiple sampling procedures have consistently identified a peak displaced from the normal morning peak as well as drifting of the rhythms over time, in at least some individuals with autism (Hill et al., 1977; Richdale and Prior, 1992). One study showed a mean earlier rise (Hill et al., 1977) whereas others found peaking later in the day (Richdale and Prior, 1992). Unfortunately, reduced cortisol levels at a given time point cannot distinguish between differences in amplitude or waveform, yet indicate an abnormal cortisol profile that would not be inconsistent with the drifting peak observed in other studies (Corbett et al., 2006, 2008; Curin et al., 2003). In sum, while results are somewhat inconclusive, children with autism appear to demonstrate cortisol profiles that differ from control subjects, even when accounting for age and intellectual functioning (Corbett et al., 2006, 2008; Curin et al., 2003; Richdale and Prior, 1992).

Melatonin is likely a better marker because it demonstrates a robust circadian rhythm, is not easily influenced by environmental or social factors (with the exception of light) and has been more directly linked to sleep. Chamberlain and Herman (1990) were the first to suggest that melatonin secretion is different in children with autism, proposing that a subgroup of those children may have a hypersecretion of the hormone. Subsequent work examining melatonin in children with autism indeed suggests abnormal melatonin production (Kulman et al., 2000; Melke et al., 2008; Nir, 1995; Ritvo et al., 1993; Tordjman et al., 2005).

An overall reduced amplitude melatonin rhythm, including diminished nocturnal values, was found in two of those studies (Kulman et al., 2000; Nir, 1995). Perhaps the most extreme findings come from Kulman et al. (2000), wherein blood samples were obtained via venous collection every four hours across a 24-h period. Not only was there a relative decreased mean nocturnal value compared to the age-matched healthy comparison group ($n = 20$), but all 14 autistic patients presented with melatonin rhythm abnormalities. Specifically, a majority of autistic subjects showed reduced differences between day and night melatonin levels. A smaller subset of subjects presented with an inverted circadian rhythm (Kulman et al., 2000), a pattern also commonly observed in those with Smith–Magenis syndrome (SMS) (Potocki et al., 2000). Parenthetically, patients with SMS often exhibit characteristic autism-like behaviors as well as sleep problems (Smith et al., 1998). In contrast, Nir and colleagues did not find circadian phase differences based on mean melatonin profiles derived as a percentage of each subject's daily mean in their smaller study ($n = 10$), but there was a dampened-amplitude melatonin rhythm in autistic subjects (1995). If data analysis had included comparisons of individuals, phase differences of certain patients with autism may have been revealed, as melatonin was found in 1/3 of patients at times in which the hormone was non-detectable in all control subjects (Nir, 1995). Such patterns underscore the importance of accounting for individual differences in phase.

Tordjman and colleagues conducted a larger controlled study, and similarly, autistic children demonstrated abnormally low nighttime 6-sulphatoxymelatonin levels (2005). They examined this major melatonin metabolite in subjects with autism ($n = 50$) and normal controls matched for age, sex and stage of puberty ($n = 88$). However, only nighttime samples of urine were collected. In addition to the fact that 63% of children with autism demonstrated 6-sulphatoxymelatonin values less than half the mean of the control group, a reduction in the metabolite was also correlated with severity of communication and play skill deficits (Tordjman et al., 2005). Pre-pubertal control subjects demonstrated relatively higher 6-sulphatoxymelatonin than older control subjects, whereas autistic subjects showed a trend in the opposite direction. Pubertal and post-pubertal subjects with autism instead showed increased nocturnal levels compared to younger children with autism (Tordjman et al., 2005). This finding, in particular, may provide evidence of a critical difference in the development of circadian rhythms in children with autism. Typical, healthy individuals show declining nocturnal melatonin levels during adolescent years (Waldhauser et al., 1988), though studies examining melatonin as a function of pubertal development specifically have yielded more inconsistent results (Arendt, 1978; Lenko et al., 1982; Penny, 1982; Silman et al., 1979).

Ritvo et al. (1993) found elevated daytime melatonin in individuals with autism, similar to other laboratories (Kulman et al., 2000; Nir, 1995); however, nocturnal melatonin values were not significantly different between groups (Ritvo et al., 1993). The fact that this study was conducted in older adolescents and young adults may be the reason for this apparent discrepancy (Ritvo et al., 1993), which is consistent with the findings of more similar nighttime melatonin values within older, post-pubertal subjects (Tordjman et al., 2005). Older autistic subjects (26–30 years old) did trend towards lower nocturnal melatonin levels in the study from Nir and colleagues (1995), although at least half of those subjects were on neuroleptic medications and/or presented with EEG abnormalities as well (Nir, 1995). Patients on neuroleptics have significantly increased enzyme activity of pineal hyrdroxyindole-O-methyltransferase, involved in melatonin synthesis, as compared to drug-free patients (Owen et al., 1983). This is the opposite of the trend reported by Nir and colleagues (1995), albeit the study of neuroleptic influence on melatonin synthesis was performed in schizophrenic and not autistic patients. Lack of parallel data in the other studies of individuals with autism does not allow for further comparison. Finally, a very recent study found lower plasma melatonin in a majority of patients with ASDs in comparison to controls at one morning time point (Melke et al., 2008). Interestingly, melatonin concentrations were reduced in the unaffected parents of those children as well. This apparent heritability may be due to an underlying genetic component as a mutation in ASMT, a gene encoding an enzyme involved in melatonin synthesis, was found in some of those with lower melatonin levels (Melke et al., 2008).

Hormone secretory patterns in children with autism are certainly altered, as indicated by the cortisol and melatonin studies described. Specific challenges to examining hormones in children with autism include difficulty gathering multiple samples across a 24-h period via methods that subjects will tolerate. Appropriate management of data also proves difficult when analyzing and interpreting overall patterns in results that contain large individual differences. Increased individual variability in hormone profiles may due to the diversity that exists within the broad spectrum of disability that comprises ASDs and/or heterogeneity in sleep behaviors. Although much of the hormonal studies were motivated by the proposed link between sleep and autism, none employed inclusion factors relating to sleep and most did not examine sleep patterns within experimental subjects. Studies instead generally assessed hormone rhythm amplitude, without regard for the phase relationship between melatonin and sleep. It is possible that all children with autism have altered melatonin levels and a subset of the population is more sensitive to the abnormalities, although such crude inclusion factors may also be partly responsible for the varied results.

Differences in the methodology and analyses employed may account for inconsistencies as well. Specifically, assay differences and collection techniques (e.g. saliva, blood, etc.) may result in variable sensitivities for detection of hormones. Questions remaining from studies to date stem from uncertainty about the

entire cortisol and melatonin profiles. Due to limited sampling and the large range in sampling intervals in many of these studies, the nature of pacemaker level involvement remains unclear. Mean results may result from any combination of general decreased amplitude, displacement and/or even complete inversion of rhythms. Certainly, each of these profile types has been observed in certain individuals (Kulman et al., 2000; Nir, 1995; Ritvo et al., 1993; Tordjman et al., 2005). Assessing melatonin levels across several days would be useful, in order to test for longer-term changes in rhythms, such as those observed in cortisol studies (Corbett et al., 2008; Richdale and Prior, 1992). Because melatonin can be acutely suppressed by light, future work must also include more rigorous control and measures of illuminance. Examining multiple circadian outputs along with light information would help determine whether circadian rhythms are misaligned with environmental signals or if there is an internal desynchronization of endogenous rhythms.

7. Impairments in entrainment

Alterations in sleep and hormonal rhythms in children with autism may, in theory, be due to impairment of entrainment mechanisms. Children with autism are subject to many variables that could potentially impact usual signals of entrainment, including hyper- and hypo-sensitivities to visual and auditory stimuli (Talay-Ongan and Wood, 2000), decreased attention to social cues (Dawson et al., 1998), and possible misalignment between circadian phase and light–dark cycles (as described earlier). Surprisingly, there are virtually no studies to determine whether those deficits extend to impairments in circadian entrainment. Co-morbidity with a variety of visual disturbances has been reported in children with autism (Scharre and Creedon, 1992; Schulman, 1994), although no work has been done to investigate functioning of non-visual responses to light or the efficacy of other zeitgebers for regulating sleep and circadian rhythms. Ritvo et al. (1988) reported abnormally low b-wave amplitudes in the electronretinograms (ERGs) of autistic subjects, with a later follow-up revealing the magnitude of reduction varies by time of day (Ritvo et al., 1993). Very recent work showing increased color perception deficits in children with autism may point to abnormalities at the photoreceptor level (Franklin et al., 2008). It is, however, premature to draw such conclusions as those findings could be attributed to many other biological and social factors. It has also been suggested that decreased attention to social cues in autistic individuals (Dawson et al., 1998) may play a role in circadian irregularities. While certainly plausible, as social cues may be particularly important zeitgebers in humans (Aschoff et al., 1971), this theory has yet to be tested empirically. Finally, the possibility was raised earlier that sleep problems deemed as behavioral in nature might represent a misalignment between circadian phase and imposed schedules, resulting in a failure to be exposed to natural environmental cues at the appropriate time. Further exploring these possible abnormalities in entrainment functions is a wide-open area of research that could yield valuable information regarding the most frequently observed sleep disturbances in children with autism.

8. Development of sleep and circadian rhythms

The development of a mature sleep–wake rhythm is a fairly well described process. Importantly, there is a rather large range of what is to be considered normal childhood sleep behavior. Likewise, significant individual differences have been reported in development of circadian rhythms, both in pre-term and full-term infants (Kennaway et al., 1992; Mirmiran and Kok, 1991; Sadeh, 1997). This section will rely heavily on generalities derived from multiple studies. Examining the timing of the development of sleep relative to the emergence of various circadian components may point to impairments in particular structures and functions in children with autism (see Table 1). An attempt will be made to relate this usual progression to the Borbély model, including how homeostatic and circadian factors may be contributing to the maturation of sleep behaviors. Development of a normal sleep pattern, with one consolidated sleep episode during the night, likely depends on the proper functioning and coordination of homeostatic and circadian components.

Typical progression of sleep behaviors in the first 11 years of life are summarized in Table 1. Newborn infants initially exhibit a polyphasic pattern of sleep, marked by multiple sleep bouts totaling ~17 h total over the course of a 24 h day (Anders et al., 1995). Day–night rhythms in activity emerge in the first few months of life (Coons and Guilleminault, 1984). The beginning alignment of homeostatic and circadian processes during this time likely underlies the observed sleep consolidation at night, as infants begin to transition to a longer nighttime sleep episode with two daytime naps and a reduced total sleep time of 15 h (Parmelee et al., 1964). Infant sleep at this stage is also characterized by a higher level of SWA earlier in contrast to later in the night (Bes et al., 1991). The emergent SWA pattern may reflect a beginning reduction in sleep propensity over the course of the night and essentially, the early appearance of homeostatic regulatory mechanisms (Salzarulo and Fagioli, 1992). Reported increases in nighttime waking at around 9 months of age might also be the result of variability in the rates of homeostatic and circadian development (Anders, 1978; Scher, 1991). By the end of the first year, infants gradually reduce to one nap per day and ~14 h total, with longer durations of continuous nighttime sleep (Iglowstein et al., 2003). At approximately 4 years of age, napping diminishes and children generally have one 11-h nighttime sleep episode (Iglowstein et al., 2003). Typical children continue to sleep ~11 h a night until they reach about 9 years of age. The observed decline in overall sleep duration from infancy to middle childhood results mainly from the elimination of daytime sleep, which is most coherent with a rapid accumulation of sleep propensity in younger children and progressively slower accumulation of sleep pressure with aging (Acebo et al., 2005). Sleep in older children continues to advance with age, but at a more modest pace relative to the dramatic changes seen during earlier years. Average nighttime sleep declines from 11.1 h at 5 years of age to 9 h by age 11 (Iglowstein et al., 2003). Changes in sleep continue through adolescence and into older adulthood. Because the focus of this review is on children, later stages of development will not be detailed here.

In contrast to the relatively protracted process of sleep maturation, a number of daily rhythms have been observed already in the human fetus, including activity, breathing and heart rate (for review, see Seron-Ferre et al., 2001a,b). Early studies suggested that diurnal rhythms found in the fetus were not endogenous but were rather driven by the mother, as newborns seemed to lack any rhythmicity (Junge, 1979; Parmelee et al., 1964; Prechtl, 1974). Subsequent studies identified observable phase differences between the mother and fetus of rodents, indicating the possibility of an independently functioning fetal clock (Jud and Albrecht, 2006; Reppert and Schwartz, 1986; Shibata and Moore, 1988). Indeed, formation of the SCN in humans (Reppert et al., 1988) as well as SCN innervation by the RHT in primates (Glotzbach et al., 1992; Hao and Rivkees, 1999) are complete by mid-gestation. In addition, mammalian studies of the fetal SCN show circadian rhythms of metabolic and genomic activity (Breen et al., 1996; Constandil et al., 1995; Reppert and Schwartz, 1984). Melatonin receptors have been found in human fetal SCN as well as other areas of the brain (Thomas et al., 2002),

yet fetal melatonin rhythms at this stage are provided by the mother (Kennaway et al., 1992; Yellon and Longo, 1988). Finally, body temperature rhythms have been observed during the first days of life in pre-term neonates, even in the absence of photic signals and temporal cues from the mother (Mirmiran and Kok, 1991; Sitka et al., 1994).

After birth, significant development of the circadian system occurs, with rhythms in activity and hormone secretion arising in the first months of life (Rivkees, 2003). Circadian rhythms of melatonin production and secretion are observed in 2–3 month old infants (Ardura et al., 2003; Kennaway et al., 1992, 1996), and cortisol rhythms become detectable around these ages as well (Antonini et al., 2000; Mantagos et al., 1998). Interestingly, the mean age of entrainment to a light–dark cycle in pre-term and term infants occurs at approximately the same stage, at 44.8 weeks post-conception (Shimada et al., 1999). Circadian melatonin rhythms and sleep consolidation during the night appear to develop together, further supporting the proposed role of this hormone in sleep (see Table 1). One study examined both melatonin rhythms and sleeping patterns in the same 6–8 month olds and found that sleep onset was associated with the rise in melatonin levels during the evening while sleep fragmentation corresponded to an inappropriate peak in melatonin (Sadeh, 1997). In sum, oscillatory functions as well as overt rhythms are present very early in life, even though different rhythms emerge at variable rates and depend on environmental factors. Lighting conditions and maternal care have been shown to affect the development of various circadian rhythms in newborns (Brandon et al., 2002; Ferber et al., 2002; Peirano et al., 2003; Rivkees, 2003, 2004; Weinert et al., 1997). Further description of circadian changes at later stages of development during childhood is lacking.

Considering that sleep and circadian rhythms demonstrate normal changes across the lifespan, understanding the typical maturation of the sleep and circadian systems may assist in understanding the nature of the sleep problems observed in children with autism more fully. For example, waking during the night is not unusual in typical children under 2 years of age (Sadeh et al., 1991) but has commonly been reported in older children with autism (Patzold et al., 1998; Richdale and Prior, 1995; Wiggs and Stores, 2004; Williams et al., 2004). Evaluating additional features that coincide with this developmental period, such as increased SWA earlier versus later into the night or hormone secretory rhythms, in autistic children with frequent nighttime waking may help determine whether sleep behaviors are wholly representative of an earlier developmental stage. Other frequently reported sleep problems in autism are more difficult to compare because imposed schedules may, in some instances, be contributing to observed patterns. Comparing sleep and circadian rhythms and patterns of emergence in autism versus typical development is still a rich area for further investigation. Unfortunately, longitudinal studies of sleep in children with autism are not yet available to determine whether reported problems represent sleep behaviors that did not mature in the usual way or rather emerged after seemingly normal development. There has been some evidence to suggest a correlation between age and presence of sleep problems in children with autism, with increased incidence of disturbances in younger children (Richdale and Prior, 1995; Taira et al., 1998). Studies examining prevalence of sleep disturbance in autistic individuals have concentrated on children aged 2–16 years old, with little information regarding older adolescents or young adults with autism. Examining sleep behaviors in older individuals with autism may help determine whether sleep difficulties persist into adulthood while serving to circumvent some of the difficulties of studying children.

A few studies have examined sleep patterns in older adolescents and young adults with autism and Asperger's syndrome (AS) via subjective report, actigraphy and polysomnography. Though the continuity of AS with high-functioning autism is debatable (Volkmar, 1998), it will be included under the general term ASDs for purposes of discussion. The first study to report sleep behavior in young adults with ASDs ($n = 20$, mean $\pm$ SD age = 27.2 ± 7.3) found a variety of sleep problems, based on sleep questionnaire, sleep diary and narrative (Tani et al., 2003). Questionnaire responses further revealed that the common difficulties in initiation and continuity of sleep had often begun early in childhood. The other two studies employed more objective measures. Øyane and Bjorvatn (2005) examined sleep in 15–25 year olds with ASDs via questionnaires, sleep diaries and actigraphy. They identified a higher prevalence of sleep problems using actigraphy relative to parental report, with a large majority of patients demonstrating significantly lower sleep efficiency (lower than 85%) or longer sleep latencies (greater than 30 min). Due to this under-reporting of existing sleep abnormalities in adolescents and young adults with autism, employing objective measures appears increasingly important within this older population. The final study utilized polysomnography to examine individuals with autism aged 16–27 and found differences in sleep, such as longer mean sleep latency, more frequent and longer duration nighttime wakings, lower sleep

Table 2
The table below examines the most commonly reported sleep problems in children with autism and makes sample predictions based on hypotheses of impairment to homeostatic, circadian or entrainment functions.

Sleep problem	Homeostatic	Circadian	Entrainment
Delayed sleep onset	– Sleep propensity accumulates too slowly	– Delay of intrinsic circadian phase – Lengthened endogenous period of the circadian clock – Dampened nighttime melatonin	– Heightened sensitivity or increased exposure to evening light – Decreased sensitivity or reduced exposure to morning light
Waking during nighttime sleep episode	– Reduced homeostatic pressure – Sleep propensity dissipates too quickly	– Misalignment of circadian and homeostatic components – Diminished strength of circadian promotion of sleep – Dampened melatonin	– Increased sensitivity or exposure to nighttime light
Early morning waking	– Sleep propensity dissipates too quickly	– Advance of intrinsic circadian phase – Shortened endogenous period of the circadian clock	– Decreased sensitivity or reduced exposure to evening light – Increased sensitivity or exposure to morning light
Research methods	– Examine SWA and theta–alpha frequencies via EEG – More specifically assess where during the sleep episode – Waking tends to occur	– Determine circadian phase of multiple rhythms (e.g. sleep–wake, melatonin, body temperature) – More specifically assess where during the sleep episode waking tends to occur – Examine patterns of light exposure	– Measure sensitivity to light via ERG or light-induced melatonin suppression tests – Examine patterns of light exposure

efficiency, increased duration of stage 1 as well as decreased non-REM and SWA sleep (Limoges et al., 2005).

Consistent findings of sleep impairment into young adulthood in individuals with ASDs, although certainly not conclusive, support the notion that the sleep problems in children do not merely represent a delay in the development of normal sleep functions. Additional work on sleep in adults with autism, including longitudinal studies of currently diagnosed children, would go a long way toward shedding light on this issue. Monitoring sleep behaviors earlier in development in siblings of children with autism may elucidate patterns of emerging sleep and circadian rhythms in children with autism. Experiments of children with autism in an environment devoid of time cues would help ascertain natural sleep preferences and may determine if these correspond to patterns observed in younger typical children and infants. Perhaps these studies could be conducted during school vacations when imposed schedules are less influential. Video recording could also be a useful tool as a minimally invasive way of further observing sleep behaviors in these children. Finally, examination of additional circadian measures in individuals with autism at a range of ages could be compared with normal development of specific overt rhythms.

9. Suggestions

Sleep disturbance can be a rather serious problem that requires identification of causal factors in order to develop appropriate treatment methods. Because there are many variables to consider within the complexities of both sleep and autism, it is challenging to interpret existing data as well as design studies that are going to yield meaningful information. Sleep problems most commonly reported in children with autism are now considered within the context of the Borbély two-process model, which was described earlier. Other models of sleep exist and may be applied in a similar manner. Table 2 hypothesizes the potential contribution of homeostatic, circadian and entrainment mechanisms to specific sleep problems, allowing predictions to be made that enable an efficient and logical course of study.

10. Summary

Chronic decrements in sleep lead to a variety of problems, regardless of the cause (Dinges, 2006, for review). It has been hypothesized that sleep disturbance may even predict autistic behaviors throughout the day (Schreck et al., 2004). This review has focused primarily on circadian disturbances because these appear to represent a large proportion of all reported problems in children with autism, based on similar patterns to well established circadian sleep disorders. Furthermore, current treatments are based on the hypothesis that impairment to the circadian system is responsible for sleep disturbance in autism (Andersen et al., 2008; Paavonen et al., 2003). While converging lines of evidence suggest circadian involvement within a subset of these children, further determination of the presence and type(s) of circadian dysfunction warrants further study. Such experiments require measures that can serve as reliable markers of circadian clock oscillatory functions. Given the impossibility of monitoring the SCN directly in humans, being able to distinguish between a disrupted or uncoupled clock is best determined via the study of multiple outputs.

Various circadian outputs have been measured in the studies described, but these have generally not assessed multiple outputs within the same individuals. Regardless of the measure, assessment at regular intervals across a 24-h period over the course of multiple days is preferable. Circadian rhythms that have been studied mostly include measures of sleep–wake patterns, but have also included examination of specific hormones. Unfortunately, there are very few studies wherein complete profiles of those hormones have been determined within individuals. Of course, there are also challenges to collecting certain data in children with autism, as mentioned earlier. Because limited work has found similar sleep problems in AS and young adults with autism, these individuals may represent more practical populations for study.

Finally, all sleep "problems" should not be treated as equivalent issues. A modicum of work has begun to investigate treatments, although a severe limitation to these studies is that there is a tendency to generalize across groups that may not have the same types of sleep problems (Andersen et al., 2008; Paavonen et al., 2003). Characterization of sleep disturbances must be a first step for inclusion in any treatment study or results are unlikely to be valid and may lead to the dismissal of a potentially effective treatment for a particular type of sleep problem. Ideally, future studies of circadian rhythms in autism should not only focus studies on children of a particular age and/or IQ range, but might also consider identifying children with similar sleep patterns. When characterizing sleep, environmental and social factors must also be taken into account, as the context of sleep patterns is critical. Particular attention should be paid to environmental cues that could serve to influence the circadian system. One environmental signal that has been largely ignored is exposure to ambient light as no work examining response to zeitgebers, such as light, could be found. Since light strongly influences circadian rhythms, information about exposure patterns should be included. Light-induced melatonin suppression tests may also be employed as a way of determining whether there is impairment somewhere along this well-established neural pathway. Further understanding the underlying mechanisms involved with sleep disturbance in children with autism will serve to better inform treatment strategies and may further our understanding of the relationship between sleep and circadian rhythms as well.

11. Conclusion

There is value to exploring the dynamic relationship between circadian rhythms and sleep via established models, recognized pathologies and as a normal course of development in order to gain further insight into the potential relevance to children with autism. It is now necessary to examine sleep studies in children with autism, with consideration of circadian influences, in an effort to better understand the underlying mechanisms and minimize the negative impact of these disturbances on both the children and their families.

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