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Sleep, brain development, and Autism Spectrum Disorders: insights from animal models

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Introduction

Sleep is an evolutionarily conserved and powerful drive found widely in the animal kingdom (Lesku et al., 2008). Although sleep loss impairs brain, immune, and metabolic function, its complete functions are still unknown (Everson et al., 1989; Greene and Siegel, 2004). One possible function of sleep is that it promotes brain development (Roffwarg et al., 1966). The amount of sleep is greatest during ages when the brain is rapidly developing. In addition, sleep amounts are maximal and/or change dramatically in terms of organization and regulation during critical periods of synaptic plasticity (Frank, 2017). Sleep and sleep loss have been shown to influence critical period plasticity, supporting a role for sleep in brain development (Frank et al., 2001) and suggesting that abnormal sleep in early life may lead to abnormal development.

Autism Spectrum Disorder (ASD) is the most prevalent neurodevelopmental disorder in the United States and it is estimated that insomnia affects 44-86% of the ASD population (Maxwell-Horn and Malow, 2017; Souders et al., 2017). Sleep problems are predictive of severity of ASD core symptoms, social deficits and repetitive behaviors, and associated behavioral issues such as tantrums and aggression (Tudor et al., 2012; Cohen et al., 2014; Veatch et al., 2017; Mazurek et al., 2019). Sleep problems impact the quality of life of both ASD individuals and their caregivers, thus it is important to understand why they are so prevalent. One possibility is that the underlying cellular and molecular abnormalities causal to ASD also produce abnormal sleep (i.e., abnormal sleep is one of many outcomes of an underlying problem). Considering the potential role of sleep in brain development and that early sleep disruption has been shown to impair social bonding in animal models (Jones et al., 2019), it is also possible that abnormal sleep plays a causal role in ASD. A third non-mutually exclusive possibility is that there is an interaction between the genetic variants linked to ASD and the role of sleep early in life, which influences both the presence of sleep problems and the severity of ASD.

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In this review, we explore the role of sleep in early life as a causal factor in ASD. First, we review fundamental steps in mammalian sleep ontogeny and regulation and how sleep influences brain development. Next, we summarize current knowledge gained from studying sleep in animal models of ASD. Ultimately, our goal is to highlight the importance of understanding the role of sleep in brain development and the use of animal models to provide mechanistic insight into the origin of sleep problems in ASD.

Fundamentals of mammalian sleep ontogeny

Changes in sleep and wake expression

The amount of sleep changes as an organism develops. In all mammals there are a number of conserved changes that occur in sleep in the perinatal period. These include changes in time spent in different sleep states, changes in sleeping brain activity, and changes in sleep and wake consolidation. Sleep states as defined using electroencephalographic recordings (EEG, see Box1) do not emerge in rats until postnatal days 12-16; and are preceded by relatively undifferentiated states termed active sleep (AS) and quiet sleep (QS) which are mostly behaviorally defined. An adultlike sleep cycle with EEG defined sleep states emerges between the second and third week of life in rodents (Frank and Heller, 1997) and around 3 months in humans (Roffwarg et al., 1966). Figure 1 shows the amount of time spent in each brain state as a function of age in both humans and rats. Neonates can spend up to fifty percent of their total time asleep in REMS (Roffwarg et al., 1966). The percentage of REMS that humans obtain in a day is largest in infant years and sharply diminishes before adulthood (Iglowstein et al., 2003). In contrast, the amount of NREMS increases slightly in the early years but remains more constant through one’s lifetime (Roffwarg et al., 1966; Frank and Heller, 1997).

Maturation of sleep regulatory mechanisms

Sleep is under both circadian and homeostatic control. Circadian rhythms determine the timing of sleep and wake in a 24-hour period while the sleep homeostat regulates the need to sleep (sleepiness) as a function of time spent awake (Achermann and Borbély, 2017). The power in the low frequency range of EEG recordings in NREMS, known as delta power, is a well-known correlate of sleep (Achermann and Borbély, 2017). In adults, delta power increases proportionately to the amount of time spent awake and decreases with subsequent NREMS (recovery sleep). However, the adult sleep regulatory mechanisms are not present at birth and mature at different rates. In rats, the circadian regulation of sleep does not begin to emerge until postnatal day 17 (P17). This is followed by the development of sleep homeostasis. For example, the increase in delta power in response to sleep deprivation does not appear until P24 in rats as shown in Figure 2 (Frank et al., 2016). Thus, the ability to regulate sleep in response to both time of day and sleep need emerge after the rapid decline in sleep amounts (in particular REMS) during early life and after both cortical neurogenesis and myelination are mostly completed. This suggests that problems regulating sleep need (falling asleep when sleepy) would likely emerge later in life, since the sleep regulatory mechanisms as defined in adults are not present until near weaning.

The role of sleep in brain development

Functional studies provide direct evidence that sleep is important for the developing brain and in particular for synaptic plasticity. Sleep has been shown to enhance cortical plasticity during the visual critical period (Frank et al., 2001). This appears to be highly dependent on REMS (Dumoulin Bridi et al., 2015). Other studies, as summarized in Table 1, have shown that REMS deprivation prolongs developmentally regulated cortical plasticity *in situ*. REMS has also been shown to increase synaptic pruning in adolescent mice (Li et al., 2017). Last, early life sleep deprivation has been shown to influence social bonding in adulthood (Jones et al., 2019). Overall these studies provide evidence that sleep contributes to brain development and that lack of sleep during early life may have long lasting effects on human behavior.

Insomnia in Autism Spectrum Disorder

Today, one in 59 children are diagnosed with ASD at age 8 (Baio et al., 2018) and it is estimated that up to 86% of this population suffers from at least one reported sleep problem (Maxwell-Horn and Malow, 2017; Souders et al., 2017). Individuals with ASD often sleep less and have problems falling and staying asleep. Insomnia in children is defined as a sleep latency longer than 30 minutes and/or frequent night awakenings that reduces sleep efficiency (the amount of time actually spent asleep in a night) and interferes with daytime functioning (Owens and Mindell, 2011). Insomnia prevalence in ASD ranges between 40 to 86% (Johnson et al., 2009; Richdale and Schreck, 2009; Maxwell-Horn and Malow, 2017; Souders et al., 2017) which is 2 to 3 times more prevalent than in typical development (Owens and Mindell, 2011). The majority of data regarding prevalence of insomnia in ASD has been collected using sleep questionnaires. However, more recent studies using actigraphy and polysomnography (PSG, which uses EEG, EMG, and heart rhythm monitoring) support the findings that ASD individuals have shorter sleep time, longer sleep latency, and decreased sleep efficiency relative to typical development (Elrod and Hood, 2015; Singh and Zimmerman, 2015). Sleep problems are predictive of severity of ASD (Tudor et al., 2012; Cohen et al., 2014; Veatch et al., 2017; Mazurek et al., 2019) and greatly impact the quality of life of both ASD individuals and their caregivers. Studies have shown that sleep problems in individuals with ASD also alter parents sleep and increase stress (Meltzer, 2008). However, why insomnia is so prevalent in ASD is unknown.

Is there a link between abnormal sleep development and ASD?—Many neurodevelopmental processes altered in ASD, such as neurogenesis, neuronal migration, synaptogenesis and synaptic plasticity (Gilbert and Man, 2017), occur at ages when sleep is the predominant brain state. In rats, neurogenesis starts at embryonic day 9.5 and is complete by P15 while myelination occurs between P10 and P20 (Semple et al., 2013); coinciding with the emergence of EEG identifiable NREMS and REMS and the maturation of sleep homeostasis. Another important process for brain development and ASD pathophysiology is the balance between excitatory and inhibitory neurotransmission, in particular the role of the neurotransmitter GABA (Coghlan et al., 2012). Abnormal GABA neurotransmission as mechanism for ASD pathogenesis has been widely studied in rodent models of Fragile X syndrome (FXS). These models exhibit extensive dampening of the GABAergic system (Paluszkiewicz et al., 2011). Although GABA is the main inhibitory

neurotransmitter in the adult brain, it can be excitatory in the immature central nervous system. This paradoxical action of GABA may help developing neurons fire together, form synapses and cortical networks. The developmental switch in GABA polarity is estimated to occur in rats in the second postnatal week (Ben-Ari et al., 2007) and has been shown to be delayed in a mouse model of FXS (He et al., 2014). Inhibitory synaptogenesis continues after the switch in polarity and is characterized by a rapid increase in synapse number and maturation that terminates around the end of the 4th postnatal week in rats (De Felipe et al., 1997). As reviewed above, all key stages of sleep ontogeny occur between the second and fourth week of life in rodents. In other words, between the GABA switch and the end of inhibitory synaptogenesis.

The timing of these events and the established role of GABA as the primary neurotransmitter of sleep promoting nuclei (Schwartz and Kilduff, 2015) raises the possibility that the development of inhibitory input into the cortex and the role of sleep in brain development are related. GABAergic interneuron development has been shown to be sensitive to sleep disruption in both kittens and young voles (Hogan et al., 2001; Jones et al., 2019). The role of sleep in forms of developmental synaptic plasticity dependent upon inhibitory circuits is well established (Frank et al., 2001). In summary, events required for normal brain development, which are altered in ASD, occur when sleep amounts are at their highest and when all fundamental aspects of sleep ontogeny and maturation occur. Therefore, sleep may have a causal role in network dysfunction in ASD. The mechanisms, however, are still unknown. The use of animal models holds great promise to uncover the mechanisms that link sleep, development and ASD.

Sleep studies in animal models of ASD—Animal models are a useful tool to understand mechanisms underlying core symptoms and co-morbid problems in ASD (Crawley, 2012). Clinically valid animal models are those that have both construct and face validity. Construct validity requires that the animal model is generated with the same underlying biological cause, e.g. the targeted mutations in the animal model replicate the causal genetic variant in the patient population. Face validity ensures that the model's behavior is analogous to the symptoms of the human disease (Chadman et al., 2009). To study sleep problems in ASD we need to use models with both construct and face validity. We focused on sleep and circadian activity studies performed in rodent models of mutations in genes that have been linked to ASD according to the Simons Foundation Autism Research Initiative (SFARI) gene database, and examined whether they showed reduced sleep time, fragmented sleep and longer latency to fall asleep. In Table 2, we report the animal models in which sleep studies were performed using EEG & EMG, the standard for analyzing sleep in mammals. There is a great amount of variability in sleep phenotypes among the different ASD rodent models. For example, the mutant rat models of CDFE (Cntnap2) show longer waking periods whereas the mutant mice show fragmented wakefulness (Thomas et al., 2017). The Neuroligin-1 knockout mice report decreased wakefulness whereas the Neuroligin-2 knockout mice have increased wakefulness and the Neuroligin-3 mutant mice have no changes in sleep state (El Helou et al., 2013; Liu et al., 2017; Thomas et al., 2017; Seok et al., 2018). It is also important to note that based on the SFARI gene evidence scores, not all genes have the same strength of evidence linking them to ASD which could be a

factor affecting the variability in data. In Table 3, we summarize published findings performed using activity monitoring to study sleep and circadian rhythms. The results were categorized by studies performed in standard light:dark conditions or studies performed in the absence of light to investigate the endogenous activity of the circadian clock. Most rodent models display total reduced activity, which could be indicative of reduced sleep. However, that could simply reflect reduced mobility. Therefore, it is hard to draw conclusions regarding sleep from studies that only use actigraphy in rodents.

Overall, among all studies that looked at sleep in rodent models using EEG, very few show reduced sleep time, sleep fragmentation and longer latency to fall asleep. The following rodent models display reduced sleep time: 16p11.2, *Shank3, Fmr1, Mecp2, Ube3a, Rims1, Scn1a, Scn8a, Disc1, Gabrb3, Nrlgn3, Camk2a, Cacna1g, Nlgn2, Npas2*. From those, only 5 (*Shank3, Ube3a, Scn1a, Disc1, Cacna1g*) reported increased sleep fragmentation. In addition, only 3 (*Shank3, Nlgn3, Cacna1g*) looked at sleep latency and only 2 (*Shank3, Cacna1g*) show an increase in latency to fall asleep. There are two possible non-mutually exclusive explanations regarding the lack of prevalence of sleep problems in ASD rodent models relative to what has been observed in the clinical population: 1) some genes linked to ASD are not linked to sleep problems 2) some of the ASD animal models do have face validity but either the sleep phenotype or some of the relevant features in regards to ASD were not evaluated.

To find animal models with both face and construct validity with the goal of unraveling the mechanisms behind sleep problems in ASD, it is important that standardized protocols and consistent criteria be used to study sleep. Figure 3 outlines an ideal protocol for conducting sleep studies in rodents. A basic protocol of sleep phenotyping needs to include at least 48 hours of continuous EEG and EMG recordings. Sleep states (NREMS, REMS and wake) should be accurately determined, which cannot be done using automated software at present. Proper quantification of sleep parameters, including time in state, sleep fragmentation, latency to sleep and spectral power, should be performed using properly powered statistics. A 24-hour baseline sleep study should be performed to assess the spontaneous sleep patterns of the animals. This should be followed up by a 24-hour sleep deprivation study. The latter should include a period of sleep deprivation (5-6 hours) and recovery sleep for the remainder of the 24 hours, to assess the animal's homeostatic response. A key component of sleep phenotyping that is missing from most studies is the study of the sleep homeostatic response. Increase latency to fall asleep is a commonly reported sleep problem in ASD, yet many of the animal models in Table 2 do not report latency to fall asleep or do so without performing sleep deprivation. Sleep latency should be evaluated following sleep deprivation. The reason is that latency can only be compared across animals if the prior wake history is the same (Mang and Franken, 2015). Sleep latency is also a marker for sleep homeostasis and should decrease with increased sleep pressure. Therefore, it is possible that some of the rodent models in Table 2 will show longer latencies to fall asleep, if the homeostatic response to sleep deprivation was evaluated.

Summary and future directions

The mechanisms underlying insomnia in ASD are still not known. Animal models are a promising tool to answer this question. To date, from the 305 rodent models of CNVs or genes considered to be linked to ASD according to the SFARI database, sleep was studied using EEG in only 22. However, most models do not show the key features of insomnia: longer latency to fall asleep, increased sleep fragmentation and reduced sleep time. As outlined in Table 2, 15 rodent models of ASD report decreases in either NREMS or REMS time, from which 5 reported fragmented sleep and 2 show increased latency to sleep, although only one study evaluated sleep latency following sleep deprivation. Therefore at present, there is only one ASD rodent model that has both construct and face validity to study sleep in ASD (Ingiosi et al., 2019). Nonetheless, can we learn something in regards to mechanisms linking sleep to ASD from some of the known mechanisms underlying the genetically determined ASD models that show reduced sleep time (14 in total)? Several interesting patterns emerge that possibly point to mechanisms by which sleep, and brain development may interact in ASD. First, a good proportion of the mouse models also present with learning and memory impairments. The relationship between sleep and learning is well documented. Sleep deprivation impairs learning and memory by inhibiting translation (Vecsey et al., 2012; Tudor et al., 2016). Sleep on the other hand promotes translation, and protein synthesis during sleep is required to consolidate cortical plasticity in vivo (Seibt et al., 2012). Aberrant protein synthesis has been proposed as one of the molecular pathways leading to ASD (Kelleher and Bear, 2008). Aberrant protein synthesis has been thoroughly characterized in the Fmr1 model. Ube3A is also known to influence protein turnover. Mecp2, Fmr1, Npas2 and Ube3A are all transcriptional/epigenetic regulators that can control how activity influences gene expression and subsequently protein levels. Although the role of epigenetics in early brain development as well as learning and memory is well established, how sleep may influence those processes has not yet been explored in depth. Therefore, the relationship between sleep, chromatin regulation and ASD is an interesting new direction of inquiry. Second, the majority of the genes are involved in synaptic function (*Shank3, Disc1, Rims1, Gabrb3, Nrlgn2, Nrlgn3, Camk2a, Scn1a, Scn8a and Cacna1g*). This is not surprising given both the established role of sleep in early life in synaptic plasticity and its disfunction in ASD. These “synaptic” genes include several classes of molecules, such as scaffolding proteins (Shank3, Disc1), adhesion molecules (Nrlgn 2 and 3), vesicle release (Rims1) ion channels (Scn1a, Scn8a, *Cacna1g*) and signaling molecules (Camk2a), indicating that sleep could influence all levels of synapse formation (or vice versa). Interestingly, only one neurotransmitter receptor mutant shows reduced sleep time: the beta subunit of the GABA a receptor (Gabrb3). As we discussed earlier, there’s a strong case to be made for the role of GABA in early development, sleep regulation and ASD. Therefore, it is reasonable to propose that GABA mediated neurotransmission is an important component of the mechanism underlying insomnia in ASD. Third, according to the Allen Brain Institute: Developing Mouse Brain Atlas, all above mentioned genes except Disc1 reach peak expression before P14. Consequently, sleep is the predominant brain state and the main source of spontaneous brain activity when these genes are maximally expressed in the brain. This is true for synaptic components and transcriptional regulators alike. This raises the question of whether sleep is required for defining the role of these genes in the establishment of synapses and networks, since activity-dependent regulation at

P14 is sleep-dependent regulation. Last, it is important to highlight the distinction between sleep and circadian effects. The gene lists between Table 2 and 3 are largely non-overlapping, mostly due to a lack of study of both phenomena in the same animal models. In cases in which both have been studied there's no clear correlation between the phenotypes. For example, Shank3, Disc1, Mep2 and Scn1a mutants sleep less, but show a reduction in total activity and no disruption in the timing of the activity. Ube3a mutants show changes in activity while Npas2 mutants show an increase. Mecp2 and Fmr1 mutants are the only ones that show a change in the timing of the activity, which would be considered a true circadian effect. These findings suggest that sleep and circadian regulating mechanisms involve a different but partially overlapping set of genes. Indeed, research supports that circadian disruption is prevalent in ASD independently of insomnia, with dysregulation in expression of circadian genes and melatonin being commonly reported (Karaivazoglou and Assimakopoulos, 2018; Carmassi et al., 2019). Overall, even though the number of rodent ASD models for which sleep has been studied is small, those studies already provide several future directions of inquiry in regard to the mechanism linking sleep, brain development and ASD.

There are important caveats that need to be taken into account when interpreting the available literature on sleep in ASD rodent models. First, all sleep phenotyping was performed using adult animals, usually only male. Since sleep is functionally important for brain development, sleep in rodent models of ASD should also be analyzed from a developmental perspective. Studies of sleep in developing animals, looking into the time periods in which homeostatic sleep regulation emerges as outlined earlier in this review, could tell us when and how these mechanisms begin to go wrong in ASD. Thus, studies should be conducted as early as possible in development so that the origins and trajectory of sleep problems can be discovered. Although there is a gender bias in ASD diagnosis, it is not clear whether there is a gender bias regarding insomnia in ASD, so in animal studies both sexes should be analyzed. Second, the role of most high-confidence ASD risk genes in terms of sleep regulation has not yet been explored. Therefore, it is possible that our understanding of the functional pathways that underlie the common mechanisms between sleep, development and ASD will change once that happens. Last, most of the animal models used to study ASD are models of syndromic forms of ASD, which makes up a small proportion of ASD cases. ASD is known to have a strong genetic component (Bai et al., 2019). However, that includes a variety of types of genetic variation in addition to genetically identifiable syndromes, including *de novo* single nucleotide and copy number variants, as well as polygenic risk that results from a combination of rare and common variants (Weiner et al., 2017). Therefore, the use of animal models that mimic rare genetic mutations to understand mechanism is inherently limited. Nonetheless further study of sleep in animal models of ASD holds great promise to understand this link and potentially find the cause and treatments for insomnia on the Autism Spectrum.

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Significance statement:

Insomnia affects up to 86% of individuals with Autism Spectrum Disorder, predicts severity of core symptoms and impacts quality of life of caregivers. In this article we highlight how understanding the role of sleep in brain development and using animal models to study mechanisms is a promising avenue to uncover the origin of sleep problems in the spectrum.

Box 1.

Fundamentals of mammalian sleep

Definition of Sleep:

Sleep is a state of reduced mobility and responsiveness to stimuli that can be easily reversed and when prevented organisms try to recover it.

Definition of sleep states:

In mammals, sleep states are traditionally defined by measuring brain activity using electroencephalogram (EEG) and muscle activity using electromyogram (EMG) (Siegel, 2009):

Wakefulness, EEG patterns of high frequency and low amplitude.

Rapid-eye-movement sleep (REMS), brain activity patterns similar to wake along with myotonia from the neck down.

Non rapid-eye-movement sleep (NREMS), brain activity patterns with low frequency and high amplitude oscillations.

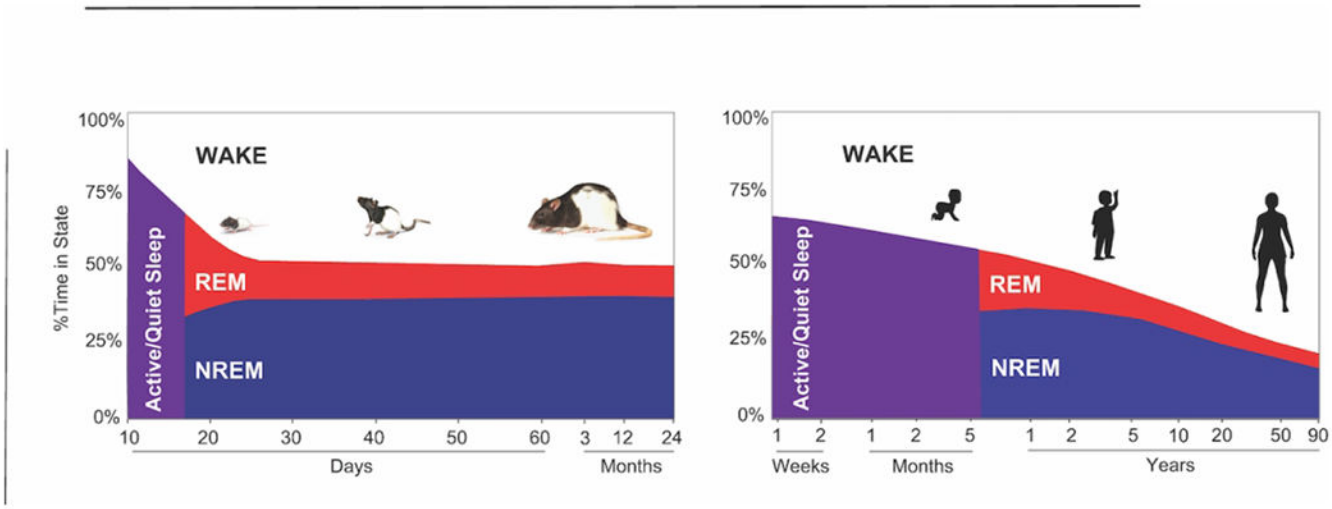

Figure 1.

Sleep time as a function of age. Percent time over 24 hours spent in wakefulness (white), rapid eye movement sleep (REMS; red) and non-rapid eye movement sleep (NREMS; blue) on the y-axis. In purple: age ranges in which sleep states are not identifiable using EEG. The x-axis represents age. On the left, sleep time across the lifespan in rats, summarizing studies at the following age ranges: P9 (Seelke and Blumberg, 2008), P12-P60 (Frank and Heller, 1997), 3-12 months (Zepelin et al., 1972). On the right, sleep time across the lifespan in humans, adapted from (Roffwarg et al., 1966).

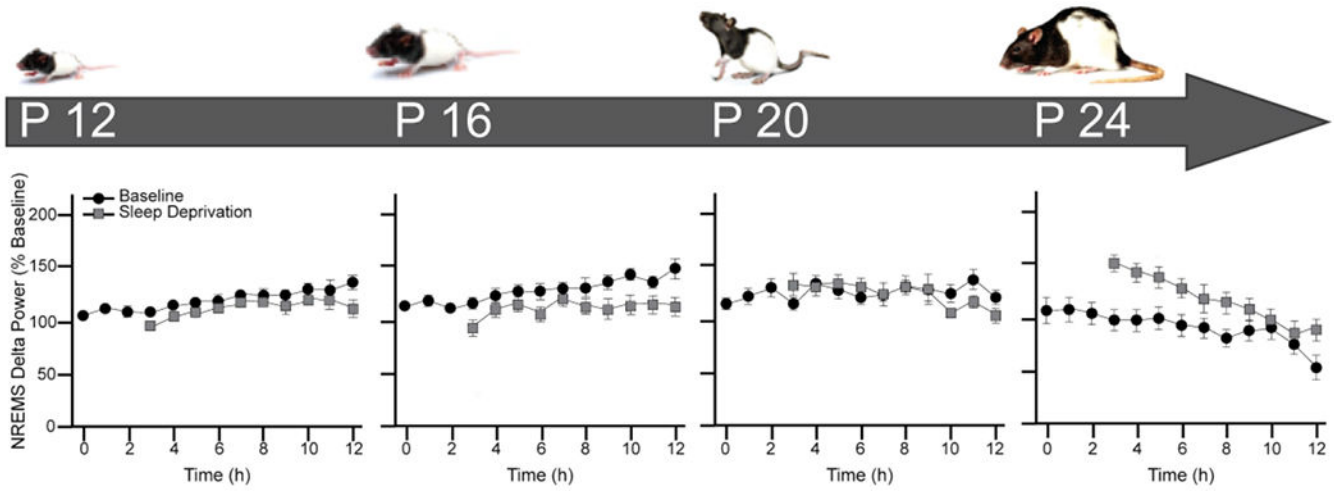

Figure 2. Timeline of development of sleep homeostasis in rats.

On top, age from birth: postnatal days 12 (P12), 16 (P16), 20 (P20) and 24 (P24) Below, graphs of changes in non-rapid eye movement sleep (NREMS) delta power (0.5-4.0Hz) after 3 hours of sleep deprivation (SD) corresponding to the different post-weaning ages (P12-P24) depicted above in developing rats. Mean ± SEM NREMS delta power is expressed as percent of the 12 hours mean NREMS delta power value before sleep deprivation at hours 0-3. Hour 0 represents the first hour of light period. Data originally reported by (Frank and Heller, 1997).

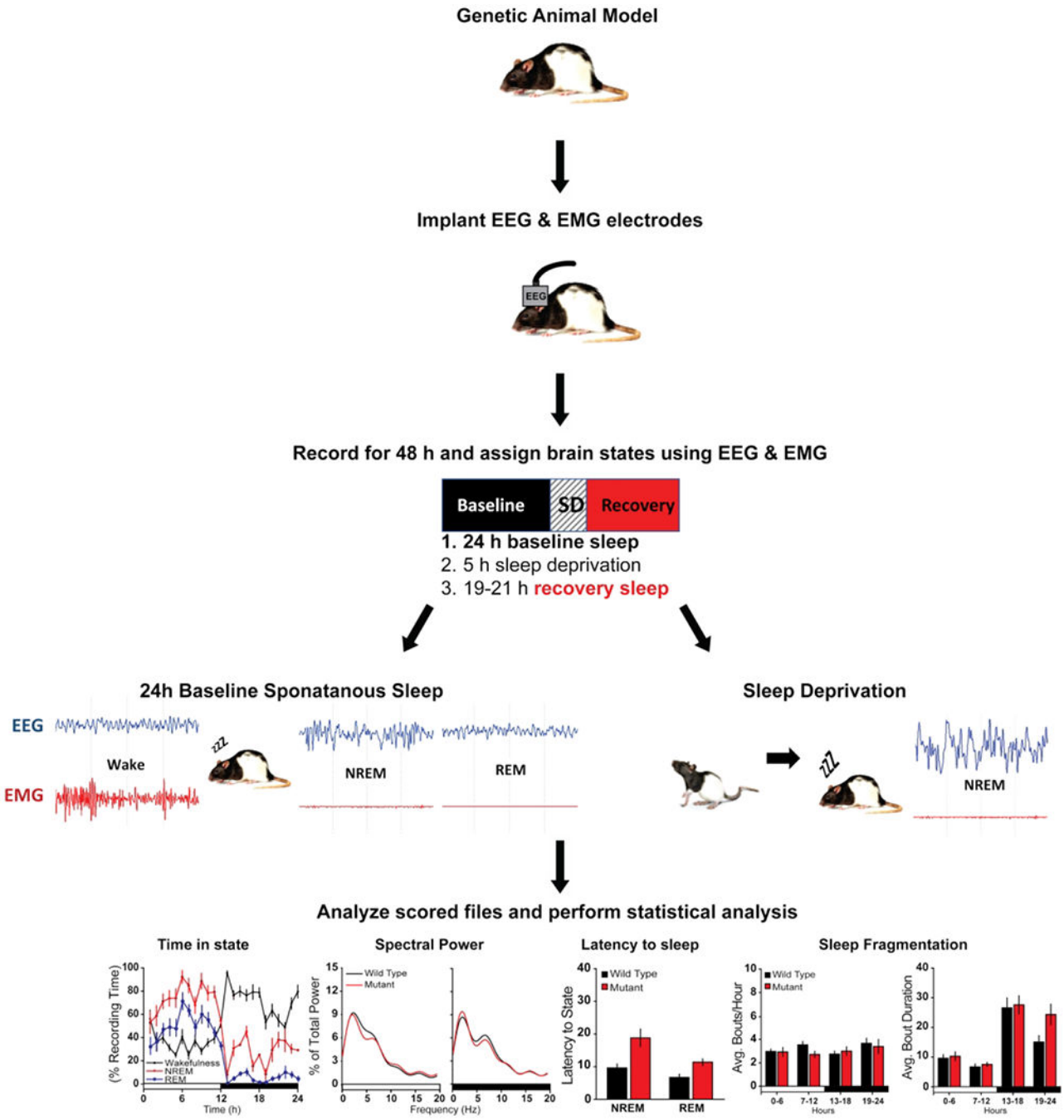

Figure 3. Outline of experimental design for sleep studies in rodent models.

Mice are implanted with electroencephalographic (EEG) and electromyographic (EMG) electrodes under anesthesia. Four EEG electrodes are placed contralaterally over frontal (2) and parietal (2) cortices, and two EMG electrodes are inserted in the nuchal muscles. Mice are allowed 5 days of recovery from surgery prior to habituation to the recording environment. After one-week habituation, mice undergo 24 hours of undisturbed baseline EEG and EMG recording starting at light onset. The next day, mice are sleep deprived (SD) for 5 hours via gentle handling beginning at light onset. Mice are then allowed 19 hours

undisturbed recovery sleep. EEG and EMG data are collected via a lightweight, counterbalanced cables, amplified, and digitized at 200 Hz using acquisition software. Wakefulness and sleep states are determined by visual inspection of the EEG waveform, EMG activity, and fast Fourier transform (FFT) analysis by an experimenter blinded to the genotype. Data is scored as wakefulness, NREMS, or REMS with 4 second resolution bins. Sleep parameters are quantified from the scored data and statistically analyzed. Required parameters for sleep characterization are as follows: time in state (wake, NREMS and REMS, baseline and SD day), spectral power for each state (baseline and SD day), latency to sleep following SD, sleep fragmentation (number of bouts in each state per hours, baseline and SD). Standardized protocol adapted from (Ingiosi et al., 2019).

Table 1.

Summary of functional studies that support the role of sleep in brain development or developmental cortical plasticity. Studies are divided into those that analyze the role of NREMS or REMS.

NREMS	REMS
NREMS enhances synaptic plasticity in the cortex of kittens (Marcos G. Frank, Issa, and Stryker 2001)	One week of REMS deprivation in immature rats prolongs the critical period for developmentally regulated synaptic plasticity (Shaffery et al. 2002)
Chronic sleep deprivation causes a decrease in hippocampal volume in adolescent rats (Novati et al. 2011)	REMS enhances experience-dependent plasticity in developing cerebral cortex in kittens (Dumoulin Bridi et al, 2015b)
	REMS prunes new formed postsynaptic dendritic spines in mouse motor cortex during development and after motor learning (Li et al. 2017)
Pharmacological sleep deprivation in rats 1-3 weeks of age results in behavioral changes and sleep disturbances into adulthood (Mirmiran 1986b) Early-life sleep disruption impairs social bonding. (Jones et el. 2019)	

Table 2.

Summary of published studies using EEG recordings to measure sleep in rodent models of ASD. Only genes and copy number variants (CNVs) reported in the Simons Foundation Autism Research Initiative gene database (SFARI GENE) are reported. Out of the 304 mouse/rat CNV/gene models reported, 22 have been used to study sleep using EEG. SFARI evidence scores categorize genes based on evidence supporting a gene's relevance to ASD risk. Categories defined by SFARI database are as follows: 1 (High Confidence), 2 (Strong Candidate), 3 (Suggestive Evidence), 4 (Minimal Evidence), 5 (Hypothesized), S (Syndromic) (Wisor et al., 2002; Dudley et al., 2003; Lee et al., 2004; Anderson et al., 2005; Colas et al., 2005; Lonart et al., 2008; Kimura et al., 2010; Papale et al., 2010, 2013; El Helou et al., 2013; Johnston et al., 2014; Zhou et al., 2014; Ehlen et al., 2015; Kalume et al., 2015; Kumar et al., 2015; Jaaro-Peled et al., 2016; Tatsuki et al., 2016; Angelakos et al., 2017; Diessler et al., 2017; Dittrich et al., 2017; Holst et al., 2017; Liu et al., 2017; Thomas et al., 2017, n.d.; Boone et al., 2018; Seok et al., 2018; Ingiosi et al., 2019; Lu et al., 2019).

CNV/Gene	PMID	SFARI Evidence Score	Total sleep time	Sleep fragmentation	Latency to sleep
16p11.2 (Mouse)	27739237	N/A	Increased wakefulness, decreased NREMS	Consolidation of wakefulness	Not reported
16p11.2 (Mouse)	30541142	N/A	Increased wakefulness, decreased REMS& NREMS	Decreased REMS bout duration and number	Not reported
Fmr1 (Mouse)	29775702	S	Decreased REMS	Decreased number of REMS bouts	Not reported
Shank3 (Mouse)	30973326	1, S	Decreased total sleep time during light and dark	Decreased REMS bouts at baseline and shorter NREMS and REMS bouts in the dark period	Increased latency to NREMS following SD
Mecp2 (Mouse)	25018705	1	No difference across 24 hours. Increased wakefulness in dark period	Shorter REMS bouts in light period, longer REMS bouts in dark period	Increased latency to NREMS at lights on
Ube3a (Mouse)	26446213	1	Decreased REMS	Decreased number of REMS bouts. Fragmented NREMS during dark period	Not reported
Ube3a (Mouse)	15921919	1	Decreased NREMS	Increased wakefulness and NREMS bouts. Decreased duration of bouts in dark period	Not reported
Cacna1c (Mouse)	25845695	1	No difference in total sleep time. Decreased REMS after SD	Increased number and shorter NREMS bouts	Not reported
Rai1 (Mouse)	28548639	1	No difference over 24 hours. Decreased wakefulness in light	Not reported	Not reported
Rims1 (Mouse)	18495360	1	Decreased NREMS in dark period. Decreased REMS in 24 hours	Decreased number of NREMS and REMS bouts	Not reported
Scn1a (Mouse)	25766678	1	No difference	Increased wakefulness bouts	Not reported
Scn1a	23311867	1	Increased wakefulness, decreased NREMS and REMS in dark period. No difference after SD	No difference	Not reported
Scn8a (Mouse)	20353942	1	Decreased wakefulness in dark period. Increased NREMS. Decreased REMS in liqht period	Decreased number and duration of REMS bouts during the light period	Not reported
Cntnap2 (Mouse)	28364455	2, S	No difference in time in state	Fragmentated wake	Decreased latency to sleep at lights on

CNV/Gene	PMID	SFARI Evidence Score	Total sleep time	Sleep fragmentation	Latency to sleep
Cntnap2 (Rat)	28364455	2, S	No difference in time in state	Consolidation of wakefulness and REMS	No difference in latency to NREMS. Increased latency to REMS lights on
Cacna1h (Mouse)	26996081	2	Decrease sleep duration	Not reported	Not reported
Disc1 (Mouse)	28720848	2	Decreased NREMS, increased REMS	Increased REMS and wakefulness bouts. Decreased REMS bout duration	No difference
Disc1 (Mouse)	27354230	2	Increased wakefulness and NREMS No difference after 2 h SD	Not reported	Not Reported
Gabrb3 (Mouse)	12419540	2	Decreased REMS during light	Decreased number of REMS bouts during light period	Not reported
Nlgn3 (Mouse)	28385162	2	No difference in time in state	No sleep fragmentation	Not reported
Nlgn3 (Rat)	28958035	2	Decreased NREMS, increased REMS during light period	Longer wake and REMS bouts. No difference in NREMS bouts	No difference in latency to NREMS o REMS at light onset
Nlgn1 (Mouse)	23716671	3	Decreased wakefulness, increased NREMS. No difference after SD	No difference	No difference at baseline or after SD
Camk2a (Mouse)	19455148	3, S	Decreased NREMS during the light period, increased REMS during the dark period. Decreased NREMS and increased REMS after SD	Not reported	Not reported
Cacna1g (Mouse)	15677322	3	Decreased NREMS	Fragmentation of NREMS	Increased latency to NREMS at light onset
Cacna1g (Mouse)	15601764	3	Decreased NREMS in light period	Longer wakefulness bouts during NREMS	No difference
Csnk1e (Mouse)	24744456	3	Increased REMS in the dark period	Decreased NREMS bouts in light period. Increased REMS bouts in dark period	Not reported
Grm5 (Mouse)	28980941	3	Increased NREMS,decreased REMS and wakefulness during light period. Increased wakefulness in dark period after SD	Not reported	Not reported
Nlgn2 (Mouse)	30231918	4	Increased wakefulness, decreased REMS. Decreased NREMS in dark	Consolidation of NREMS bouts in light period and consolidation of wakefulness in dark period	Not reported
Npas2 (Mouse)	12843397	4	Decreased NREMS and REMS in dark period	Not reported	Not reported

Table 3.

Summary of published studies using activity monitoring in 12:12 hours light:dark cycle and in the absence of light to measure sleep and circadian rhythms in rodent models of ASD. Only genes and copy number variants (CNVs) reported in the Simons Foundation Autism Research Initiative gene database (SFARI GENE) are reported. Out of the 304 mouse/rat CNV/gene models reported, 17 have been used to study circadian rhythms. SFARI evidence scores categorize genes based on evidence supporting a gene's relevance to ASD risk. Categories defined by SFARI database are as follows: 1 (High Confidence), 2 (Strong Candidate), 3 (Suggestive Evidence), 4 (Minimal Evidence), 5 (Hypothesized), S (Syndromic) (Zheng et al., 2001; Dudley et al., 2003; Meredith et al., 2006; Kozlov et al., 2007; Zhang et al., 2008; Sahar et al., 2011; Han et al., 2012; Wither et al., 2012; Lacaria et al., 2013, 2013, 2013 p.1; Ehlen et al., 2015; Kalume et al., 2015; Li et al., 2015; Tsuchiya et al., 2015; Jaaro-Peled et al., 2016; Diessler et al., 2017; Lipton et al., 2017; Saré et al., 2017; Ingiosi et al., 2019).

CNV/Gene	PMID	SFARI Evidence	Activity monitoring in 12:12 h light:dark cycle	Activity monitoring in the absence of light
17p11.2 (Mouse)	23703963	N/A	Reduced total running wheel activity	Reduced free running period length. Reduced total running wheel activity
Shank3 (Mouse)	30973326	1, S	Reduced amplitude of running wheel activity	Reduced amplitude of running wheel activity with normal period length
Fmr1 (Mouse)	28919851	S	Shorter sleep duration in light period under homecage activity monitoring	Not recorded
Fmr1 (Mouse)	18589395	S	Fmr1 and Fxr2 knock out mice show no difference in wheel running compared to wild types. Fmr1/Fxr2 double knock out mice show loss of rhythmic activity	Fmr1 and Fxr2 knock out mice show shorter-free running period in constant dark and loss of rhythmic activity. Fmr1/Fxr2 double knock our mice show loss rhythmic activity
Tsc1andTsc2 (Mouse)	28746872	1	No difference in wheel running activity	Shorter free running period with no change in circadian amplitude or overall activity
Ube3a (Mouse)	26446213	1	No difference in circadian period or overall activity	No difference in circadian period or overall activity
Mecp2 (Mouse)	26456390	1	No difference in circadian rhythm	No difference in period length. Decrease in wheel running activity
Mecp2 (Mouse)	25779967	1	Reduced total wheel running activity, reduced alpha length and increased fragmentation of wheel running	Reduced total wheel running activity. Increase in-free running period length, decreased alpha length and increased fragmentation of wheel running
Mecp2 (Mouse)	22523589	1	Decrease in activity bout length but no difference in number of bouts (home cage activity monitoring)	Not reported
Rai1 (Mouse)	28548639	1	Decreased overall running wheel activity, decreased running wheel activity in the light period	Increase phase advance and increase in alpha length
Rai1 (Mouse)	23703963	1	Decrease total running wheel activity	Decreased period length and decreased total running wheel activity
Scn1a (Mouse)	22223655	1	Delayed phase of activity onset. Reduced total wheel running activity	Increased period length. Reduced total wheel running activity
Scn1a (Mouse)	25766678	1	Reduced total wheel running activity	Reduced total wheel running activity
Disc1 (Mouse)	27354230	2	Decreased activity during the dark period	No difference in circadian period
Magel2 (Mouse)	17893678	2, S	No difference in wheel running activity	Reduced amplitude of running wheel activity with reduced activity in the subjective dark period

CNV/Gene	PMID	SFARI Evidence	Activity monitoring in 12:12 h light:dark cycle	Activity monitoring in the absence of light
Cd38 (Mouse)	21937766	3	Reduced total locomotor activity	Shorter period length
Kcnma1 (Mouse)	16845385	3	Decreased amplitude of locomotor activity	Increase in period length. Decreased amplitude of locomotor activity
Npas2 (Mouse)	12843397	4	Increased running wheel activity during the dark period	Shorter period length
Per1 & Per2 (Mouse)	11389837	4	No difference in wheel running activity	PER1 mutants have a shorter period length. PER1 mutants and PER1/PER2 double mutants have no circadian rhythm
Rasd1 (Mouse)	23703963	5	No difference in wheel running	Female mice displayed reduced free running period lengths