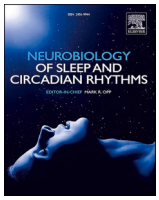
Neurobiology of Sleep and Circadian Rhythms 14 (2023) 100085

Contents lists available at ScienceDirect

Neurobiology of Sleep and Circadian Rhythms

journal homepage: www.elsevier.com/locate/



Loss of sleep when it is needed most – Consequences of persistent developmental sleep disruption: A scoping review of rodent models

Noah E.P. Milman [a,b], Carolyn E. Tinsley [a,b], Ravikiran M. Raju [c,d], Miranda M. Lim [a,b,*]

[a] Oregon Health and Science University, Dept. of Behavioral and Systems Neuroscience, Portland, OR, 97214, USA
[b] Veterans Affairs Portland Health Care System, Portland, OR, 97214, USA
[c] Picower Institute for Learning and Memory, Massachusetts Institute of Technology, Cambridge, MA, 02139, USA
[d] Division of Newborn Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA, 02115, USA

ARTICLE INFO

Keywords:
Method of Sleep Disruption
Cage manipulation
Gentle handling
Autism
Social behavior
Plasticity

ABSTRACT

Sleep is an essential component of development. Developmental sleep disruption (DSD) impacts brain maturation and has been associated with significant consequences on socio-emotional development. In humans, poor sleep during infancy and adolescence affects neurodevelopmental outcomes and may be a risk factor for the development of autism spectrum disorder (ASD) or other neuropsychiatric illness. Given the wide-reaching and enduring consequences of DSD, identifying underlying mechanisms is critical to best inform interventions with translational capacity. In rodents, studies have identified some mechanisms and neural circuits by which DSD causes later social, emotional, sensorimotor, and cognitive changes. However, these studies spanned methodological differences, including different developmental timepoints for both sleep disruption and testing, different DSD paradigms, and even different rodent species. In this scoping review on DSD in rodents, we synthesize these various studies into a cohesive framework to identify common neural mechanisms underlying DSD-induced dysfunction in brain and behavior. Ultimately, this review serves the goal to inform the generation of novel translational interventions for human developmental disorders featuring sleep disruption.

1. Purpose of this review

While it is clear that sleep is critical for normal brain development, and several studies in rodents have examined the consequences of developmental sleep disruption (DSD) on later life behavior, to our knowledge, no single review has synthesized findings from DSD rodent models across the varied developmental time points and methodologies. Thus, we present this scoping review to synthesize common findings across diverse paradigms and developmental timepoints to better inform future studies. For inclusion in this scoping review, we considered paradigms in rodents which directly impacted or led to disrupted post-natal sleep between birth and late adolescence, or ~2 months of age (N = 34 in total; Tables 1 and 2). This rodent developmental period roughly corresponds to birth through the first 15 years of human life (Spear, 2000). This cohesive framework will help to identify common neural mechanisms underlying DSD-induced changes in brain and behavior, with the goal of generating translational interventions for human developmental disorders.

2. Introduction: Function of normal sleep in development

Depending on the particular window of development, sleep impacts the maturation of both brain and behavior and potentially contributes to phenotypes seen in neurodevelopmental disorders. As the primary objective of this review is to highlight dysfunction, we cite notable reviews in the field to guide readers to more detailed assessments of typical function.

2.1. How sleep changes over development

2.1.1. Human studies

Sleep is a fundamental biological process with unique importance in development. Dynamic changes in sleep amount and features of sleep electroencephalogram (EEG) are associated with changes in brain maturation (Colrain and Baker, 2011). The amounts of non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep are at their lifetime maximum during the first few days to weeks of life

Abbreviations: DSD, Developmental Sleep Disruption; ASD, Autism Spectrum Disorder; P, postnatal day.

* Corresponding author. Portland VA Health Care System, P3-RD42 3710 SW US Veterans Hospital Rd, Portland, OR, 97239, USA.
E-mail address: lmir@ohsu.edu (M.M. Lim).

https://doi.org/10.1016/j.nbscr.2022.100085
Received 25 September 2022; Received in revised form 22 November 2022; Accepted 23 November 2022
Available online 6 December 2022

(Roffwarg et al., 1966), become consolidated (fewer awakenings) around the second year of life (Paavonen et al., 2020), and subsequently decline with age (Ohayon et al., 2004). NREM delta power, a purported measure of homeostatic sleep drive, declines after a brief increase between age 6 to 8, and has been hypothesized to support pruning of synapses during development as well as myelination of axons (Tarokh and Carskadon, 2010; Feinberg and Campbell, 2013; Kurth et al., 2017). These changes in NREM delta power or slow wave activity coincide with structural brain growth (Buchmann et al., 2011). Normative changes in sleep architecture and spectra over the course of development have been shown to underlie individual differences in brain maturation, emotional regulation, and cognition, (for detailed review of the clinical literature (Mason et al., 2021; Tarokh et al., 2016)).

2.1.2. Rodent studies: electrophysiological signatures

While human studies have reported associations between sleep at various developmental time points and brain maturation, socio-emotional learning and cognition, they remain largely correlational. Rodent models allow the ability to precisely manipulate sleep during specific developmental windows, and attribute causality to perturbations. Although some aspects of rodent sleep differ from humans, rodents exhibit similar ultradian rhythms and generate NREM and REM sleep based on similarly stereotyped EEG/electromyogram (EEG/EMG) signals. The organization of the sleep cycle (wake-quiet sleep-active sleep) is clearly apparent in 9 day old rat pups while delta activity appears on postnatal day 11 (P11) and theta activity at P13 (Graphical Abstract 3a) (Seelke and Blumberg, 2008). Sleep bout durations increase from P2 to P21 with each week of life in developing rats (Blumberg et al., 2004). Serial EEG assessment of sleep and wake across the second postnatal week of life in mice reveals greater consistency of EEG spectral activity, fewer transitions in behavioral state and a decline in time spent in REM sleep (Rensing et al., 2018) (Graphical Abstract 1a). Between P23 and P29, wildtype (WT) mice spend less time in NREM and REM in the dark period, and theta power in wake and REM decreases steadily (Medina et al., 2022). Throughout this period, the brain continues to mature, REM sleep serves to promote this maturation and plasticity in later development (Mirmiran, 1995).

2.1.3. Rodent studies: sensorimotor development

Early life sleep contributes to the development of sensorimotor systems. A recent review conveys three conceptual frameworks for experience-dependent development – highlighting the role of sleep in modulating this maturation (Blumberg et al., 2022). Briefly, myoclonic twitches that occur during REM (or active sleep) early in life promote the development of the sensorimotor and cortico-hippocampal system (for detailed review (Blumberg et al., 2020)). Specifically, at P8, neurons in the primary motor cortex rely on input from forelimb twitches occurring during sleep but this responsiveness changes to wake by P11 (Dooley and Blumberg, 2018). REM sleep enables proper circuity wiring underlying rhythmic activity measured by coherence between barrel cortex and hippocampus at P8 (Dooley and Blumberg, 2018; del Rio-Bermudez et al., 2020). There is activity of non-motor regions during sleep in developing rats as well, including prefrontal cortex, suggesting the diffuse influence of infant sleep (Gómez et al., 2022). Spindle bursts within the primary somatosensory cortex during the first week of life in rats support the formation of E/I balance and rely upon myoclonic twitching (Marcano-Reik et al., 2010). Thus, in summary, it appears that REM sleep during specific periods in development serves to drive muscle twitches important for proper neural circuit development.

2.2. Functions of sleep in development

2.2.1. Human studies: overview

Human infants undergo associative learning during sleep, even at very early ages (Nelson et al., 2013). Studies have shown that early life sleep phenotypes predicted later language development and cognition, and poor sleep co-occurs with mental illness and social deficits in adolescence (Frank et al., 1998; Feng et al., 2001; Reeb-Sutherland et al., 2011). Conversely, stable sleep-wake transitions and high REM-activity in premature neonates showed improved cognitive and emotional development compared to those without (Shellhaas et al., 2022; Tesler et al., 2013). In otherwise healthy pre-term infants, both reduced night sleep at 36 weeks gestational age measured via actigraphy and quality of home environment via questionnaire predicted achievement of developmental milestones, suggesting that early-life sleep and environmental factors are crucial determinants of later mental development (Veatch et al., 2017).

2.2.2. Rodent studies: acute sleep deprivation impacts neural plasticity

Early development is characterized by excessive synapse formation, and thus, synaptic pruning and maintenance is critical for the development of mature and functional circuits (Graphical Abstract 3a) (Weisman et al., 2011; Arditi-Babchuk et al., 2009). Using *in vivo* tracking of newly formed synapses over time in three week old mice, REM sleep deprivation for 8 h reduced the amount of new spine elimination compared to no-deprivation or NREM deprivation (Weisman et al., 2011). The size of remaining spines increases in no-deprivation or NREM deprivation, suggesting a role for REM sleep in maintaining newly formed syanpses (Weisman et al., 2011). Following motor learning, sleep in 1-month old mice supports generation of dendritic filopodia which become spines in layer 5 pyramidal cells (Gertner et al., 2002). Acute sleep deprivation in 1-month old mice increases synapse density in the hippocampus and decreases spine elimination in the cortex (Li et al., 2017; Changeux and Danchin, 1976).

During sleep, a distinct process called homeostatic down-scaling of synaptic strength occurs, subserving higher order functions such as learning and memory consolidation (Adler et al., 2021; Spano et al., 2019; Zhou et al., 2020). One hypothesis is that synapses are potentiated through wakeful experiences, while sleep serves to reduce synaptic strength (for review (Zhou et al., 2020)). A series of studies found that sleep modifies the structural space between the presynaptic and post-synaptic nerve terminals, indicative of synaptic strength. Acute sleep deprivation in two week old mice prevented synaptic renormalization, the processes of synaptic downscaling (Diering et al., 2017).

One such model of sleep-dependent neuronal plasticity deserves specific mention is monocular deprivation (MD) studies. During a sensitive developmental window, one eye is occluded, and cortical reorganization occurs such that the neural response in binocular cortex of the deprived eye is decreased and increased in the open eye, known as "ocular dominance plasticity" (ODP). Importantly, ODP depends on prior sensory experience (de Vivo et al., 2017, 2019; Tononi and Cirelli, 2014; Frank et al., 2001). MD leads to dendritic spine loss in layer 5 of primary visual cortex and frontal association area, respectively, in 1-month old mice, both of which effects are abolished with REM or total-sleep deprivation (Changeux and Danchin, 1976). Consistent with similar studies conducted in kittens (de Vivo et al., 2017), subsequent studies in 1-month old rodents have found specific cells and layers preferentially affected, including apical dendrites in layer 5 and layers 2/3 excitatory neurons (Changeux and Danchin, 1976; Tononi and Cirelli, 2014). In this issue, Renouard and colleagues show sleep opportunity supports ODP – sleep increases activity associated with the exposed eye and reduces activity in the deprived-eye (Tononi and Cirelli, 2014). In summary, these studies demonstrate that sleep in early development promotes synaptic reorganization and neuronal plasticity.

Finally, a recent systematic review of the animal literature created a mechanistic mathematical model and found that the function of sleep switches from neural reorganization (synaptic maintenance and myelination) to neural repair (clearance of metabolites) estimated around 2.4 years of age in humans (Renouard et al., 2022). Maintenance of spines as discussed above is consistent with this model in which neural reorganization preferentially occurs during REM sleep prior to the human equivalent of 2.4 years of age.

2.3. Rodent models of developmental sleep disruption

2.3.1. Overview

With an understanding of normative sleep in development, it is equally important to consider translational models of sleep disruption. Rodents are useful models to characterize the relative contribution of distinct periods of life whereby sleep underlies behavioral and brain function (Graphical Abstract b). Because of the high overlap with phenotypes of neurodevelopmental disorders, the field has primarily considered the impact of developmental sleep disruption (DSD) on social, anxiety-like, and sensorimotor behavior. Sleep loss during this period can negatively impact prefrontal, somatosensory, midbrain and hippocampal circuitry which dysregulates behavior. DSD and neurodevelopmental disorders show strikingly similar neuropathological profiles, most notably alterations to synaptic plasticity (Graphical Abstract 3b). This bolsters the hypothesis that human neurodevelopmental disorders may be driven in part by DSD.

2.3.2. Acute sleep deprivation provokes a homeostatic response

Physiologically, sleep loss normally generates a homeostatic response, which could be represented as an increase in total, NREM or REM sleep time or continuity, and/or NREM delta power (Miyamoto et al., 2003). These features are best provoked through additional sleep challenges, 3-h sleep deprivation generates increased sleep time and continuity in P12–P20 rats, though delta power only increases beginning at P24 (Ribeiro et al., 1999). WT mice expectedly show increased sleep across development (serially assessed between P23 – P59) following 3-h of sleep deprivation (Medina et al., 2022). The amount of REM-rebound following deprivation also increases with developmental age (from 2-week old to 4-week old) (Cao et al., 2020). These features are characterized in acute sleep deprivation studies, conversely, chronic sleep disruption may or may not show clear sleep rebound and is the focus of this review.

2.3.3. Methods of sleep disruption

There are four primary modalities of disrupting sleep in development in rodents, 1) manipulation of the cage environment, 2) manipulation or handling of the animal directly, 3) pharmacological manipulation, and 4) genetic manipulation (Fig. 1, Tables 1 and 2). Cage manipulation includes cage-shaking using an orbital shaker (Jones et al., 2019a; Lord et al., 2022) or insertion of novel objects to force locomotion (Li et al., 2017). Cage manipulation presents the opportunity for potential automated disruption that is either continuous, targeting only the light-phase (when rodents are most likely to be asleep), and/or using closed loop delivery of disruption based on EEG/EMG activity (Jones et al., 2019a, 2019b, 2020, 2021; Lord et al., 2022; Bian et al., 2022; Feng et al., 2000; Nagai et al., 2021). An animal's cage includes its light source, the developmental chronic circadian disruption (DCCD) paradigm mimics severe shift-work with the light cycle advances dramatically every other or every fourth day (Smarr et al., 2017; Ameen et al., 2022). Animal manipulation involves either gentle handling (Medina et al., 2022; Weisman et al., 2011; Saré et al., 2016, 2019, 2022a; Araujo et al., 2018; Yang et al., 2012; Murack et al., 2021) when the animal enters a sleep state, placing the animal on a platform over water where they are required to stay awake to avoid falling into the water (da Silva Rocha-Lopes et al., 2018; Shaffery et al., 2006; Shaffery et al., 2002; Chen et al., 2015), or installing a sweeping bar that moves through the cage to enforce wakefulness (Wallace et al., 2015; Atrooz et al., 2019). Pharmacological manipulation involves administration of a drug (e.g. chlorimipramine (monoamine reuptake blocker)) for the purpose of increasing wakefulness at the expense of REM and/or NREM sleep (Mirmiran et al., 1981, 1983). The four modalities of DSD are distinguished in Fig. 1 and in detail in Table 1 (cage, pharmacological and genetic manipulation) and Table 2 (animal manipulation).

While this review focused on postnatal DSD, a few notable studies of genetic models of neurodevelopmental disorders have shown striking parallels to findings seen in classic DSD paradigms. Genetic manipulation includes creation of transgenic animals with mutant circadian clock expression (Liu et al., 2022; Singla et al., 2022) or risk genes for

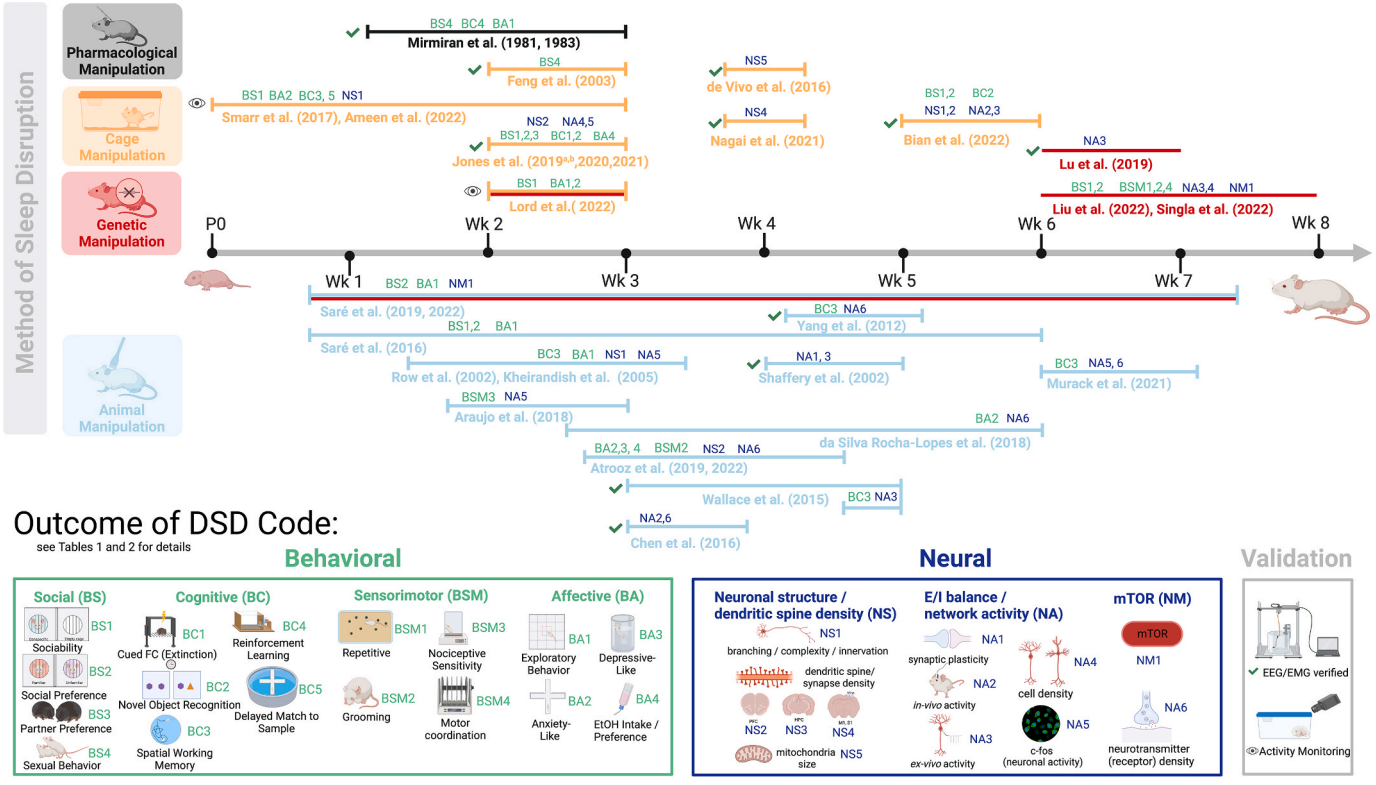


Fig. 1. Consequences of developmental sleep disruption in rodent models, a roadmap.

neurodevelopmental disorders, (Medina et al., 2022; Saré et al., 2017, 2022a). Circadian clock gene mutations have been implicated in ASD, thought to contribute to sleep-wake and social dysfunction (reviewed by (Lorsung et al., 2021)). *Bmal1* is a master regulator of the circadian clock; it forms a heterodimer with *CLOCK* and activates the transcription of other clock genes. *Bmal1*$^{-/-}$ mice demonstrated increased NREM sleep amount with EEG/EMG recordings at 10–12 weeks of age, which could not be rescued with restored expression of *Bmal* in the brain (Christopher Ehlen et al., 2017). Notably, characterization of the sleep phenotype in *Bmal1*$^{-/-}$ or *Bmal1*$^{+/-}$ in the context of development is lacking. *Shank3*$^{\Delta C}$ is a mutant form of the Shank3 gene with exon 21 truncated and an established model of ASD. Shank3$^{\Delta C}$ mice showed reduced time asleep at juvenile (P25-41) and adolescent (P42-56) timepoints, using a piezo home-cage monitoring system as a proxy for sleep phenotyping (Lord et al., 2022). Using EEG/EMG recordings, *Shank3*$^{\Delta C}$ mice showed less total sleep across development with increased amounts of REM sleep than controls at P23, P29, P59 in the light phase, accompanied by reductions in NREM sleep (Medina et al., 2022). When challenged with a sleep deprivation protocol, *Shank3*$^{\Delta C}$ mice at P30 showed longer latency to recovery sleep, thought to be consistent with an insomnia phenotype common in ASD. Unlike WT development, *Shank3*$^{\Delta C}$ animals did not demonstrate age-related changes in spectral power, including no change in theta power between P23 and P59 in wake and REM sleep. *Fmr1* is a human gene that is responsible for Fragile X syndrome, which is the most common genetically encoded intellectual disability. In a mouse model of Fragile X syndrome using *Fmr1*$^{y/-}$ males, there are late emerging (P70 and P180) deficits in sleep time in the light phase but not at developmental timepoint of P21 (Saré et al., 2017). Human chromosome 16p11.2 microdeletion is related to social and language developmental delay, a mouse model of this abnormality showed reduced REM and NREM sleep in early adolescence (6–7 weeks of age) (Lu et al., 2019). In summary, a variety of genetically modified mouse models exist that lend support to the hypothesis that a bidirectional relationship exists between sleep and neurodevelopmental disorders. Furthermore, these studies may also provide insight into gene-environment interactions, highlighting sleep quality as a potential critical mediator (reviewed in-depth elsewhere (Missig et al., 2020)).

2.3.4. Considerations of methodological variability

It is important to recognize that each of these paradigms has their own caveats and limitations. During sleep manipulations, not all studies validated DSD with the gold standard EEG/EMG recordings. Some paradigms were validated based on video scoring or cage-activity, finding differences in rest (bout) duration, but without EEG-based sleep staging (Lord et al., 2022; Ameen et al., 2022). The timing and duration of sleep disruption is also an important consideration in assessing the behavioral and neuropathological consequences. Some paradigms adhered to a specific, well-justified period of development (Lord et al., 2022), whereas others spanned multiple stages of development (Saré et al., 2019). When comparing different manipulations, it will be essential to keep in mind the exact developmental window under study (Fig. 1). Unlike adult sleep disruption paradigms reviewed elsewhere (Zamore and Veasey, 2022), early-life paradigms must work in the context of developmental constraints in a pre-weaned cage: maintaining parental care, pup survival and physical growth, and limiting stress. Studies that sufficiently account for these constraints, and/or include a stress group as a control (Jones et al., 2019a; Lord et al., 2022; Bian et al., 2022; Shaffery et al., 2006; Saré et al., 2022b), can differentiate their paradigm from an early-life stress protocol and more precisely investigate the impact of early-life sleep disruption. Notably, gentle handling has been shown to increase corticosterone levels in young rats aged P12–P20 with as little as 70 min to 3 h of handling according to age (Hairston et al., 2001). Evidence from adult rats suggests that corticosterone levels during sleep disruption may contribute to differential response to sleep loss (Machado et al., 2013). Metyrapone treatment (inhibitor of corticosterone synthesis) during four days of REM sleep disruption reduced the number of awakenings compared to saline injected controls and reduced slow wave activity compared to corticosterone treated animals which dampened the expected rebound. DSD paradigms which characterize changes in corticosterone during the paradigm itself, or after a period of time have been noted in Tables 1 and 2 Finally, pharmacological and genetic manipulations are certain to have off-target effects on development beyond sleep.

3. Behavioral consequences of developmental sleep disruption

A series of national and international surveys over the last few decades recognize that children are not getting enough sleep which is associated with mood disturbances, risk taking behavior, obesity, and impaired executive function (Owens et al., 2014). Unresolved sleep problems in children aged 5–17 tract with changes in socio-emotional behavior and predict behavioral difficulties later in life (Wang et al., 2016). Sleep routine is one of many changes experienced by children because of the COVID-19 pandemic, a meta-analysis found children and adolescents were the second most affected by sleep disturbances behind those infected with COVID-19 (Jahrami et al., 2022).

In addition to these associations, there is a high overlap between neurodevelopmental disorders and sleep disturbances, though the directionality is unclear (Verhoeff et al., 2018; Veatch et al., 2021). While ASD is diagnosed based on a set of core behavioral criteria (deficits in social communication/interaction and restrictive, repetitive behavior), subjective and objective sleep disturbances have been reported in both adolescents and children with ASD (Missig et al., 2020; Díaz-Román et al., 2018). Disturbances manifest in increased sleep latency (Martínez-Cayuelas et al., 2022), reduced REM sleep time (Buckley et al., 2010) and parental report of worse sleep quality (Anders et al., 2011; MacDuffie et al., 2020), resulting in substantial consequences on daytime functioning (Anders et al., 2012). Developmental trajectories may also be influenced by genetic etiology or the timing of birth, highlighting the complex pathophysiology (Heavner and Smith, 2020; Hadaya et al., 2022). Thus, disrupting sleep at different timepoints in development or rodent models may align with different aspects of the progression of these disorders.

Because of the nature of clinical research, particularly in a sensitive population like children, there is a reliance on subjective measures and longitudinal tracking can be difficult. On the other hand, rodent studies can directly probe this causal association with careful behavioral paradigms. Disruption paradigms can be employed to characterize a specific period of development with pre-determined outcomes. Our review is organized around specific behaviors impacted by DSD (some of which are species-specific behaviors), while highlighting different methods of DSD and timepoints studied across development – all of which factors may limit direct comparisons between studies.

3.1. Social behavior

To begin, social dysfunction is reviewed because of its translational importance in neurodevelopmental disorders (Arakawa, 2020). Testing social behaviors in rodents typically involve a multi chambered apparatus where animals are free to explore and/or interact with their choice of conspecifics or a combination of conspecifics and inanimate objects. These tests allow researchers to examine both sociability and social preference (including social novelty and partner preference). Sociability is a measure of a rodent's propensity to interact with a conspecific (either same or opposite sex, depending on the test) over an inanimate object or empty chamber. Social behavior can also be quantified by reciprocal social interactions in a single chamber. Social preference, on the other hand, measures the subject's preference for a novel animal compared to a "familiar" animal and requires intact social memory. Degree of familiarity and sex of the stimulus animals can be manipulated based on the inherent preferences of the species tested. Mice and rats are

Table 1
Consequences of Persistent Developmental Sleep Disruption in Rodents using Cage, Pharmacological or Genetic Manipulation.

citation Reference	Animal and Sex	DSD Timepoint	DSD Method	Sleep Validation and Impact	Behavioral Outcome in DSD group (timpoint)	Neural Outcome in DSD group (timepoint)	Cort. / Stress Validation	Notes
[55]Smarr et al. (2017)	mice	P0-P21	DCCD: 6hr / 4 days	Not Reported	↓ sociability, ↑ stereotyped behavior in EPM (P60-74)		does not mimic early life stress	
[56]Ameen et al. (2022)	mice	P0-P21	DCCD 8hr / 2 days	activity monitoring: reduced period	↓ time and entries in open arms, ↑ time to target quadrant in MWM, ↑ errors and latency to platform in DMS task (P90-110)	↓neuronal complexity in mPFC, dHPC: ↓ branching order and dendritic length (P90)	above (prior publication)	unclear translational relevance
[47,49,52,53]Jones et al. (2019[a,b], 2020, 2021)	prairie voles	P14-21	ACS: 100 rpm for 10s every 109s	EEG/EMG: ↓ REM time, fragmented NREM	↓ preference for partner (P100 ♂), ↓ NOR, ↑ EtOH intake in 2BC (P80). ↓ cued FC extinction: slower and less complete, ↓ LTM (P75-90).	↑ dendritic spine density in PL L2/3, ↑ immature spines in L2/3 of PL, IL (P80). ↓ vGLUT1 in presynaptic and spine area of PL (P80-100). ↑ PV+ interneurons in S1 (P100). ↑ c-fos after footshock in CeA and LA of AMG (P85).	no change	
[25]Feng et al. (2003)	rats ♂	P14-P21	ACS: detected REM = 5s shake	EEG/EMG: ↓ REM time	↑ latency to mount, ↓ aggressive behavior (P90)			↑ NREM sleep, not specific to REM
[54]Nagai et al. (2021) [120]de Vivo et al. (2016)	mice	P26-P30	novel stimuli + lights off 6hr light phase	EEG/EMG: ↓ NREM 68% ↓ REM 79%		↑ ASI in L2 M1, S1. ↑ density of spines w/o a synapse vs. wake ↑ size of mitochondria in frontal ctx, ↑ density of 2° lysosomes (P30)		acknowledge potential stress
[50]Bian et al. (2022)	mice	P35-42	ACS: random push 4hr/day in light phase	EEG/EMG: ↓ NREM and REM time	↓ SNP, ↓NOR (P56). ↓ sociability (P84). ↑ SNP in Shank3 InsG3680 w/ P35-42 flupirtine/opto/chemogenetic treatment (P56).	↓ novelty-dependent VTA dopaminergic Ca2+ activity, NAc dopamine release during social interaction. ↑ VTA innervation of NAc, ↓ VTA innervation of pyramidal neurons mPFC (P56)	no change	
[48]Lord et al. (2022)	mice	P14-21	ACS in *Shank3ΔC*: 100 rpm for 10s every 109s	activity monitoring: ↓ TST	↓ sociability. ↓ auditory PPI. ↓ activity in the OF (P70 ♂). ↑ time in open arms, ↓ SNP (P70 ♀). ↓ SNP in P56-P63 disrupted (P70 ♀ + ♂).		no change	compared to WT animals who underwent same DSD protocol
[69,70]Mirmiran et al. (1981,1983)	rats ♂	P8-21	clonidine (noradrenergic agonist) or chlorimipramine (monoamine reuptake blocker)	EEG/EMG: ↓ REM sleep	↓ exploration of center in OF, dysregulated sexual behavior: ↓ mounts , impaired differential reinforcement of low response rate (P70+).	↓ cerebral ctx weight (clompramine) (8 months). ↓ cerebral ctx weight (clonidine) (3.5 months).		
[76]Lu et al. (2019)	mice ♂	x	16p11.2 microdeletion	EEG/EMG: disrupted TST, NREM, REM	↓ TST, NREM and REM sleep. ↓ theta power during night REM and wake, daytime NREM slow-wave activity (P42-49).	↓ resting membrane potential and membrane resistance of vlPAG-projecting GABAergic LPGi neurons (P42-49).		
[71]Liu et al. (2022)	mice	x	*Bmal1* mutant mice	Not Reported	↓ sociability in 3-chamber and reciprocal interaction. ↑ spontaneous and induced grooming, repetetive routes, ↓ latency to fall on rotarod (P42-56).	cerebellum: ↑ Purkinjie cell density, ↑ spines, specifically immature spines. ↓ EPSC amplitude and ↑ IPSC of Purkinjie cells with ↓ spontaneous spike rate. upregulated p-S6 on mTORC1 pathway (P42-56).		
[72]Singla et al. (2022)	mice	x	*Bmal1*$^{+/-}$ mutants	Not Reported	↑ USVs after brief maternal separation (P7, P14). ↓ sociability and SNP. ↑ marbles buried, bouts of spontaneous and induced grooming. ↓ time in center, hyperactivity in OF, worse motor learning (P42-56).	↑ p-S6 protein levels in cerebellum and forebrain (P42-56).		
[73]Saré et al. (2017)	mice ♂	P21, P70, P180	*Fmr1 KO*, *Fmr1* KO/*Fxr2* Het	activity monitoring	Fmr1 KO ↓ sleep in light phase (P70 & P180). Fmr1 KO / Fxr2 Het ↓ sleep in light phase (P70).			

Study investigated male and females unless otherwise indicated with "♂", meaning males only

Abbreviations:

METHOD
DCCD: Developmental Chronic Circadian Disruption (light advance)
ACS: Automated Cage Shaking

BEHAVIOR
FC: Fear Conditioning
SNP: Social Novelty Preference
MWM: Morris Water Maze
2BC: 2-Bottle Choice
NOR: Novel Object Recognition
DMS: Delay Match-To-Sample
OF: Open Field
USV: ultrasonic vocalizations

NEURAL
Ctx: Cortex
GR: Glucocorticoid receptor
IL and PL: Infralimbic and Prelimbic Cortex
S1: Somatosensory Cortex
VTA: Ventral Tegmental Area
ASI: axon-spine interface

typically tested with same sex animals that they have been exposed to for 5–10 min (social novelty preference) (Kaidanovich-Beilin et al., 2010; Moy et al., 2004), and prairie voles are typically tested with opposite sex animals that they have co-housed with for up to 24 h (partner preference) (Beery, 2021; Williams et al., 1992). Some researchers, particularly in the context of neurodevelopment, record ultrasonic vocalizations at multiple timepoints to capture potential signs of dysregulated early social communication, while others see it as a by-product of crying (Michetti, 2012; Blumberg and Sokoloff, 2001).

3.1.1. Sociability and social interaction

We reviewed 11 studies in mice, rats, and prairie voles where sociability was tested after developmental sleep disruption. While results are mixed, the impact of DSD on sociability may depend on the

Table 2
Consequences of Persistent Developmental Sleep Disruption in Rodents using Animal Manipulation.

citation Reference	Animal and Sex	DSD Timepoint	DSD Method	Sleep Validation and Impact	Behavioral Outcome in DSD group (timpoint)	Neural Outcome in DSD group (timepoint)	Cort. / Stress Validation	Notes
[57]Saré et al. (2016)	mice	P5-42	GH 3hr/day	Not Reported/Later Timepoint activity monitoring: no change (P111)	↑ sociability (P43). no SNP (P72 ♂). ↑ SNP (P72 ♀). hypoactivity in the OF (P44).		handled controls 10'/day	controls show unexpected social behavior: ♀ are hyposocial. ♂ do not show SNP
[58]Saré et al. (2019)	mice ♂	P5-52	GH 3hr/day	Not Reported/Later Timepoint activity monitoring: no change (P74)	hypoactivity in the OF (P42, P84). no SNP (P48, P90).	↑ p-S6 protein expression across six brain regions (P94).	NS: control ↑ cort vs. stress (44%) and SR (20%) (P42)	control did not show intact sociability or SNP. Unexpected cort. Trends.
[110]Row et al. (2002) [111]Kheirandish et al. (2005)	rats	P10-24	Intermittent Hypoxia 10% O_2 every 90s	Not Reported	↑ latency and path length to platform in MWM (P25). hyperactivity in OF (P32 ♂). no improvement across trials in MWM (P120-150 ♂).	↓ complexity of neurons in CA1 (P150 ♂). ↑ neuroepinephrine in PFC (P150).		↓ body weight (P21).
[60]Araujo et al. (2018)	mice	P12-21	GH 2hr/day + novel objects	Not Reported	↑ nociceptive sensitivity (hot-plate test: ↓ paw withdrawal threshold) (P35).	↓ c-fos in periaqueductal gray. no change in S1 thickness (P35)	↑ cort. (P21).	
[63]da Silva Rocha-Lopes et al. (	rats ♂	P18-42	MPoW: $1hr^{P19-20}$ $18hr^{P21-42}$	Not Reported (citation)	↓ time in open arms (P49).	↑ BDNF in dHPC, ↑ 5-HT in dHPC, ↑ Noradrenaline in vHPC (P49).	↑ basal cort (P49).	↓ body weight
[68,116]Atrooz et al. (2019, 2022)	rats ♂	P19-32	SB: $6hr^{P19-20}$ $8hr^{P29-32}$	Not Reported	↓ time, entries in open arms, (P33, P60). ↓ entries into light area, ↓ grooming after sucrose splash (P33).↑ EtOH preference in 2BC (P39). ↑ immobility in FS (P90).	↑ IL-6 in PFC. ↓ GluA1, GluN2b. ↓ PSD-95 (P33, P90).		
[67]Wallace et al. (2015)	mice ♂	P21-35 or P32-35	SB: 12hr or 24hr	EEG/EMG, activity monitoring: ↓ NREM, REM bout length, ↑ arousability	↑ path length in MWM in acute sleep disrupted (P35).	↓ EPSP amplitude and slope in acute sleep disrupted from hippocampal Schaffer collaterals (P35+).	no change	
[66]Chen et al. (2015)	rats ♂	P21-26	MPoW 24hr	EEG/EMG for sleep deprivation paradigm		↓ pineal gland signaling and melatonin biosynthesis (P120).		
[64,65]Shaffery et al. (2002, 2006)	rats ♂	P28-35 or P37-60 (age) for 7-10d	MPoW 24hr	EEG/EMG: ↓ REM (pilot experiments)		induced LTP after TBS stimulation of WM/L VI when recording from L 2/3 of V1. enlarged hypothalamus (weight) (P35). LTP instead of LTD after LFS to WM of V1 (P45-P70).	no change	↓ body weight of sleep restricted
[61]Yang et al. (2012)	rats ♂	P29-36 or P72-79	GH + novel objects 4hr/light phase	EEG/EMG: ↓ NREM, TST	↑ distance to platform, ↓ platform crossings in MWM (P31-44).	↓ 5-HT, dopamine in hypothalamus. ↓ 5-HT, noepinephrine in midbrain. ↓ dopamine in Striatum. ↑ noepinephrine in brainstem (P36).		
[62]Murack et al. (2021)	mice	P42-50 or P70-78	GH 4hr/light phase	Not Reported (citation)	↑ immobility, ↓ latency to mobility (P50).	↓ # of 5-HT1A expressing cells in ACC and IL (P50). ↓ GR expressing cells in CA1, ↑ in PL (P50 ♀).↑ c-fos in IL, PL (P50).	↑ cort. (P50, P78♀)	↓ weight gain in all restricted groups
[58]Saré et al. (2022)	mice ♂	P5-52	GH 3hr/day in *Fmr1* KO	Not Reported/Later Timepoint activity monitoring: no change (P74)	hypoactivity in OF (P42). No SNP (P48).	↓ MBP in striatum (P94).	no change	controls do not have SNP. cort. findings imply no diff. btw. stressed/ sleep restricted
[15]Medina et al. (2022)	mice	P23, P29, P45, P49, P90	3hr GH in *Shank3ΔC*	EEG/EMG - response to sleep deprivation	↑ latency to recovery sleep - NREM (P30). ↓ NREM (P29). ↑ REM across development, no change in theta pwr (P23-59).			

Study investigated male and females unless otherwise indicated with "♂", meaning males only

Abbreviations:

METHOD
GH: Gentle Handling
SB: Sweeping Bar
MPoW: Multiple platforms over water

BEHAVIOR
FC: Fear Conditioning
SNP: Social Novelty Preference
MWM: Morris Water Maze
2BC: 2-Bottle Choice
NOR: Novel Object Recognition
DMS: Delay Match-To-Sample
OF: OF
FS: Forced Swim

NEURAL
BDNF: Brain derived neurotrophic factor
GR: Glucocorticoid receptor
S1: Somatosensory Cortex
MBP: myelin basic protein
LFS: Low frequency stimulation
TBS: Theta Burst Stimulation
WM: White Matter

developmental timing of both sleep disruption and testing, the interval between sleep disruption and testing, sex, and/or sleep disruption protocol.

Studies that directly manipulated the animal did not report a change in same-sex sociability. The sweeping bar method in of male rats for 6–8 h per day according to age, between P19-33 did not impact same-sex sociability compared to controls when tested at P33, P60, or P90 (Atrooz et al., 2019). Gentle handling of WT male mice for 3 h a day from P5-42 did not impact same-sex sociability based on time sniffing the conspecific at P48 or P90 [59]. In the *Fmr1* model of Fragile X syndrome, gentle handling from P5-52 also showed no change in sociability in males at P48 and P90 (Saré et al., 2022a). Both these groups studied males and used multiple timepoints of social testing, which may impact outcomes after multiple rounds of testing in the same animal.

Multiple chronic developmental sleep disruption protocols involving automated cage shaking have been found to reduce sociability in both mice and prairie voles when tested during adulthood. In a three-chamber assay in the highly social wild rodent prairie vole, adult animals that underwent sleep disruption from P14-21 were tested (~P100) and showed a reduction in overall time spent huddling with the opposite-sex conspecifics, suggesting a deficit in sociability in both males and females (Jones et al., 2019a). Using an identical cage shaking protocol from P14-21 in the *Shank3*$^{\Delta C}$ heterozygous mouse model of ASD, Lord and colleagues show male-specific impairment in sociability in adulthood (P70-120) compared to WT controls who underwent the same sleep disruption (Lord et al., 2022). Importantly, these alterations are unique to sleep disruption between P14-21, there was no deficit in sociability when cage shaking occurred between P56-63 (Lord et al., 2022). Bian and colleagues also found that sleep disruption using automated cage shaking in mice (closed loop EEG) between P35-42 impaired same-sex sociability at a similar adult time point (P84) in both males and females but found no difference in sociability when tested shortly after disruption in young adults (P56) (Bian et al., 2022). Consistent between Lord and Bian, is a lapse in time (≥6 weeks) between sleep disruption and changes in sociability. Future work should determine whether this is because of developmental age or the time between sleep disruption and behavioral testing. Bian and colleagues did not find any effect of adolescent sleep disruption on time interacting with a novel opposite-sex conspecific, at P56, however sexual behavior was not evaluated (Bian et al., 2022).

Circadian biology can have a marked impact on social behavior in lieu of EEG-based sleep phenotypes. Similar same-sex sociability impairments have been observed following developmental chronic circadian disruption in early adulthood (P60-74). In a modified assay with two chambers, with one containing a novel same-sex conspecific, Smarr and colleagues find chronically shifted male and female mice showed impaired sociability – spending less time interacting with a conspecific (Smarr et al., 2017). Global deletion of *Bmal1* and heterozygous *Bmal1*$^{+/-}$ mice lead to reduced sociability in males and females in a three-chamber assay between P42–P56 and *Bmal*$^{-/-}$ showed reduced reciprocal social interactions in a single chamber[71,72]. As pups (P14), both mouse models display increased numbers of ultrasonic vocalizations when briefly separated from their mothers compared to WT controls (Singla et al., 2022).

Taken together, these findings indicate developmental sleep loss at a wide range of early life time points can impair adult sociability, particularly when tested in older animals. Whether this is because of older developmental age or increased time interval that has elapsed since sleep manipulation remains to be tested. It remains possible that the method of developmental sleep disruption plays a role in the later development of sociability in adulthood. Both cage and genetic manipulations produce more robust impairments in sociability results compared to animal manipulation, perhaps through enhanced control of sleep-wake states or other methodological considerations.

3.1.2. Social preference: social novelty preference and partner preference

In contrast to the sociability assays described above, social preference testing requires subjects to choose between two conspecifics of differing degrees of familiarity. In the socially monogamous prairie vole, both males and females will typically display a preference to show affiliative behavior towards a familiar opposite sex "partner" over an unfamiliar opposite sex "stranger". This is tested in the laboratory with the widely used three-chambered partner preference test (Beery, 2021; Beery et al., 2021). Early life sleep disruption using an automated cage-shaking protocol between P14-21 in prairie voles results in impaired partner-preference in adult (~P100) males, where they do not show a preference to huddle with their partner (Jones et al., 2019a). Notably, this sleep disruption protocol does not impair partner preference behavior in female prairie voles (Jones et al., 2019a). Mice, on the other hand, prefer social novelty and in similar 3-chambered tests will typically show increased interaction time, measured by either proximity or sniffing behavior, with stranger mice compared to familiar mice (Moy et al., 2004). Bian and colleagues found that automated sleep disruption in mice from P35-42 reduced social novelty preference in both sexes when testing occurred at P56, and at P84 [50]. P5-52 gentle handling leads to the absence of social novelty preference based on time sniffing the novel conspecific in adult males at P90 [59].

The effects of developmental sleep disruption on social preference testing when genetic modification is involved are mixed. Lord and colleagues found that automated cage shaking from P14-21 in *Shank3*$^{\Delta C}$ mice abolished social novelty preference in female but not male mice. However, when sleep disruption occurred at a later time point, from P56-63, novelty preference was impaired in both males and females when animals were tested shortly after ~ P70 [48]. *Bmal* $^{\pm}$ but not global deletion of *Bmal1* in 6–8 week old C57BL/6 male and female mice impaired social novelty preference (Liu et al., 2022; Singla et al., 2022). Sleep bi-directionally modifies adult social behavior; in the *Shank3 InsG3680* autism mouse model, selectively improving NREM sleep between P35-42 with flupirtine (which opens KCNQ2/KCNQ3 K^+ channels and acts as a NMDAR antagonist) rescued impaired social novelty preference (Bian et al., 2022).

One possible explanation for deficits in social preference testing is a deficit in social memory. If social memory is impaired, the test animal may not recognize the "familiar" conspecific due to acute memory loss and the assay is non-specific for social behavior. Two of the studies described here explicitly tested social memory in developmentally sleep disrupted animals and both found intact social memory (Jones et al., 2019a; Bian et al., 2022). Bian and colleagues found intact memory in a single stimulus paradigm – sleep deprived mice lose interest in the conspecific following 30 min wait after an initial 5 min of interaction (Bian et al., 2022). However, they find that when a second novel stimulus is tested, sleep deprived animals fail to shift attention to the second stimulus from the first stimulus (Bian et al., 2022). Jones and colleagues also found intact social memory in prairie voles using a modified habituation-dishabituation paradigm. Both control and sleep disrupted male and female voles were able to increase investigation of a novel olfactory cue from a second animal after habituating to a first animal's scent (Jones et al., 2019a). Both social memory assays were conducted several weeks after the conclusion of developmental sleep disruption. It is important to note that it remains possible that sleep disruption results in acute social memory impairments as sleep promotes social-memory consolidation (Oliva et al., 2020), which may explain impaired social preference behavior when testing is conducted shortly after DSD (Lord et al., 2022; Saré et al., 2022b). These studies suggest sleep loss during early life impairs expression of adult social novelty preference, a fundamental behavior in rodents. This finding is not isolated to a single rodent model or disruption paradigm suggesting the second to fifth week is a sensitive window for the development of social novelty. Absence of novelty preference can also be viewed as the preference for familiarity, another phenotype in ASD, this association should be explored further (Krüttner et al., 2022).

3.1.3. Sexual behavior and aggression

Another way to investigate social behavior is to place two animals in a novel cage together – examining sexual or aggressive behavior. REM sleep deprivation through an automated cage shaking system between P14-21 in rats impairs adult sexual behavior and reduced offensive and increased defensive stereotyped behavior following intermittent shock when interacting with a conspecific rat (Feng and Ma, 2003). In this specific protocol, there was an increase in NREM sleep in the disrupted animals, potentially confounding the interpretation of the study. Prairie voles who underwent sleep disruption from P14-21 report no change in aggressive behavior towards opposite sex conspecifics in either sex (Jones et al., 2019a). A series of pharmacological manipulation studies from Mirmiran and colleagues shows the pharmacological suppression of REM sleep with the drug chlorimipramine from P8-21 in rats creates

dysfunctional sexual behavior (increased latency to mount and fewer ejaculations) (Mirmiran et al., 1981, 1983). No studies have explored female sexual behavior. Though few studies have comprehensively characterized sexual and aggressive behavior following developmental sleep disruption, it appears REM-specific disruption can modulate these outcomes.

3.2. Sensorimotor

Sensorimotor disturbances, including restricted and repetitive movements or aberrant reactivity to sensory inputs are common in ASD and can be investigated in translational models (Lord et al., 2018; Orefice, 2020). Self-grooming, either spontaneous or provoked by tactile stimulus or marble-burying task examine stereotyped motions. One measure of altered sensitivity is pre-pulse inhibition, which assesses sensory gating: the decrease response to a higher-amplitude stimulus that follows an initial lower-amplitude stimulus (pre-pulse). This can be measured in multiple sensory modalities (e.g. tactile, auditory) or with a single modality. Enhanced tactile pre-pulse inhibition is present in multiple genetic models of ASD and some models show altered auditory pre-pulse inhibition (Orefice et al., 2016).

The effects of developmental sleep disruption on sensory gating in rodents is mixed and may depend on species and/or developmental age at testing. Jones et al. found that prairie voles who underwent sleep disruption between P14-21 using automatic cage shaking showed no difference in auditory pre-pulse inhibition compared to non-sleep disrupted controls when tested in adolescence at P40 (Jones et al., 2019b). Using an identical cage shaking method of developmental sleep disruption, Lord et al. found that *Shank3*$^{\Delta C}$ male mice who underwent P14-21 ELSD showed suppressed auditory pre-pulse inhibition at volumes higher than 82 dB, meaning that pre-pulse is no longer able to inhibit the startle response, though testing occurred in adulthood (>P70) (Lord et al., 2022). Of note, both studies used 120 dB startle response to measure sensory gating with pre-pulse inhibition and results may vary with either tactile or mixed sensory modalities.

There is evidence that developmental sleep disruption modifies pain sensitivity in adolescence but not adulthood. Araujo et al. found that gentle handling 2hr per day from P12-21 increased tactile sensitivity, lowering the withdrawal threshold on a hot plate at P35 in males and females but not in adulthood (P90) (Araujo et al., 2018). Other common sensorimotor tasks include rotarod testing which quantifies motor learning - the duration of time an animal can last on a rotating rod, and marble burying, an assay of repetitive behavior (Angoa-Pérez et al., 2013). Adult (~P80) *Shank3*$^{\Delta C}$ male and female mice who underwent sleep disruption using automated cage shaking from P14–P21 showed normal behavior in the marble burying assay and rotarod test compared to WT sleep-disrupted animals (Lord et al., 2022). Chronic gentle handling from P5-42 found no change in rotarod testing or marbles buried in early adulthood (P74-75) (Saré et al., 2016). *Bmal1* KO and heterozygous *Bmal1*$^{+/-}$ mice show increased grooming behavior, reduced latency to fall in rotarod testing and increased number of marbles buried, giving credence to de novo circadian clock alterations in neurodevelopmental disorders with respect to impaired sensorimotor behavior (Liu et al., 2022; Singla et al., 2022). The DCCD paradigm in mice leads to increased stereotypic behavior (scored as repetitive behavior in the EPM) in adulthood (~P60-74) (Smarr et al., 2017). Bian and colleagues report no change in repetitive-restricted behavior indexed by self-grooming behavior (Bian et al., 2022).

Taken together, there is insufficient evidence to suggest any major effect of cage or animal manipulation on sensorimotor deficits. However, genetic mutation of *Bmal1* and circadian disruption through light advances appear to selectively impact sensorimotor function among studies covered in this review. Considering the overlap with phenotypes in models of ASD, repetitive behavior is a candidate behavior that all DSD paradigms should assay in future work with species and timepoint in mind. Considering the development of the motor cortex relies on sleep (particularly in the first two weeks) (Gómez et al., 2021), it is possible that DSD paradigms that apply to pre-weaned animals as opposed to later in development may have more impact on sensorimotor behavior.

3.3. Cognition

Changes in cognition following sleep loss in human adolescents are well documented but relatively unexplored in rodent DSD paradigms (Mason et al., 2021). Changes in performance on novel-object recognition, a measure of an animal's intact memory to interact with novel stimuli and Morris-Water Maze (MWM), which measures spatial memory is dependent on the hippocampus. Delayed match-to-sample task involves placing a plus maze in a water bath with a hidden platform at the end of one arm, animals are required to find the platform over trials and days of training. Acute (24-hr for 3 days) sleep disruption in P32 but not chronic (12-hr for 2 weeks) animal disruption beginning at P21 increased distance to the hidden platform in WMW, suggesting worsened spatial working memory (Wallace et al., 2015). A week of gentle handling between P29-35 lead to increased latency to find the platform in the MWM in rats aged P31-44 (Yang et al., 2012). A DCCD protocol with 8 h light shifts every other day from P0–P22 worsens performance in the MWM task: increased latency to the platform as well as the platform in a delayed match-to-sample task (Ameen et al., 2022). Intermittent hypoxia (IH), a model of obstructive sleep apnea, exposure from P10-24 in rats leads to deficits in performance in Morris Water Maze, increased time and distance to the platform in adolescence (Row et al., 2002). When this behavior is assessed in adulthood (4–5 month old rats) after exposure from P10-24, exposed male rats do not exhibit learning, neither latency to platform nor distance improve after repeated trials (Kheirandish et al., 2005). Suppression of REM sleep from P8-21 in rats worsened performance in a reinforcement learning task in adulthood (Mirmiran et al., 1981).

While novel-object recognition depends on hippocampal function, cued-fear conditioning and extinction require amygdala and prefrontal cortex (Klavir et al., 2017; Cohen and Stackman, 2015). Automated shaking protocols between P14-21 in prairie voles as well as between P35-42 in mice lead to deficits in novel object recognition at P80 and P56 respectively (Jones et al., 2019a; Bian et al., 2022). DCCD in mice did not lead to any difference in novel object recognition in early-adulthood (P60-74) (Smarr et al., 2017). Early life sleep disruption from P14-21 in male and female prairie voles also impairs cognitive flexibility in adulthood (P90-110), animals have slower extinguishing of their freezing response in cued-fear conditioning and showed heightened freezing in a long-term memory test, showing a deficit in prefrontal cortex function (Jones et al., 2021). Though both depend on hippocampal function, spatial working memory is impaired in animal manipulation studies while cage manipulation disrupts novel object recognition.

3.4. Affective changes

Affective changes may in part explain changes in social or cognitive behaviors through stress-induction or lowered motivation. These changes can be assessed in a variety of behavioral assays that characterize an animal's response to a stressful situation. Rodents typically find open or elevated spaces and brightly light areas aversive – concentrating their time in more comfortable locations but can also explore novel environments (Carola et al., 2002). Anxiety-like behavior is typically quantified in rodents using either an open field, light/dark box, or elevated plus maze. Open field testing involves placing an animal in a novel testing apparatus, where center avoidance is considered anxiety-like behavior. Light-dark testing involves a partition in a box with one side enclosed creating a dark environment which is preferred by the animal, reduced time exploring the light side is considered anxiety. Likewise, in an elevated plus maze, two arms of four ("+") are walled in while the others are open, avoiding entry or limited time in the

open arms signifies anxiety. Depressive-like behavior can be quantified in rodents with the forced swim test, animals are placed into a water bath and time until immobility (considered "giving-up") is scored. Corticosterone is a physiological measure of stress measured in the blood and can be assayed during the sleep disruption paradigm or at the time of behavioral testing. Increased corticosterone during the former would indicate the paradigm itself is stressful while the latter would suggest long-lasting stress from developmental sleep disruption.

Gentle handling 4 h at beginning of light phase from P42-50 but not P70-78 lead to increased immobility duration and reduced latency to immobility in the forced swim task on the last day of the protocol in both males and females (Murack et al., 2021). Interestingly, corticosterone was increased in females, but not males after 30 min of restraint the day after the end of both gentle handling protocols. The sweeping bar method for 6–8 h per day between P19-33 in male rats also increased immobility in the forced swim task, at P90 but not at earlier timepoints, P33 or P60 (Atrooz et al., 2019). This protocol found reduced time in the light chamber in the light/dark test at P33, reduced time and entries in open arms at P33 and P60, pointing to a wide-reaching impact of early sleep on anxiety-like behavior. Though this study characterized neuronal stress markers (p38 MAPK phosphorylation) and pro-inflammatory markers, both increased after sleep disruption, one shortcoming of the study is the lack of assessment of corticosterone from the DSD protocol. 2-hours of gentle handling from P12-21 in mice increased corticosterone levels compared to controls and maternal-separation group (Araujo et al., 2018).

In prairie voles, Jones and colleagues report no changes in anxiety-like behavior with the light/dark assay in adulthood (~P90) (Jones et al., 2019a). Bian and colleagues report no changes in anxiety based on latency to open arm in elevated plus maze in adulthood (P70-84) (Bian et al., 2022). Conversely, cage disruption in *Shank3*$^{\Delta C}$ animals generates female specific anxiety phenotypes – a maladaptive increased time in the open arms of an elevated plus maze (Lord et al., 2022). Chronic handling from P5-42 as well as automated-cage shaking in *Shank3*$^{\Delta C}$ male mice leads to hypoactivity in the open field in adulthood, an indicator of a depressive-like state (Lord et al., 2022; Saré et al., 2016, 2019). Pharmacological REM reduction in development reduces exploratory behavior in the open field – fewer entries into the center, indicating an anxiety-like trait (Mirmiran et al., 1981). IH exposure from P10-24 leads to hyperactivity in the open field of 30 day old male rats (Row et al., 2002). *Bmal1* ± mice were averse to the center of the open field, and were hyperactive in the periphery, indicated a dysregulated response to a novel environment (Singla et al., 2022). Multiple platforms over water in rats between P21-42 showed reduced time and arm entries in the EPM as well as a basal increase in corticosterone one-week after the end of the disruption protocol (da Silva Rocha-Lopes et al., 2018). These studies demonstrate developmental sleep disruption leads to a maladaptive response to a novel environment.

Though the human literature on sleep loss and risk-taking behavior is detailed, less is known about the consequences of developmental sleep disruption. Early-life sleep disruption may impact drug-seeking behavior as assayed by 2-bottle choice task between ethanol and water. In prairie voles, early life sleep disruption followed by exposure to a stressor (foot-shock) in adulthood (P80) induced increased 10% ethanol intake but there were no differences in intake at baseline (Jones et al., 2020). In rats who underwent automated disruption P19-33, there was increased consumption and preference for 5% ethanol at P39 (Atrooz et al., 2022). Primarily these studies differ in the timepoint of assessment, one in adolescence and another in adulthood.

Developmental sleep disruption shows mixed evidence on anxiety-like behavior, effects are seen predominantly through an aversion to exploring novel environments. Sleep disruption paradigms which require experimenter interaction with animals (direct animal manipulation) tend to increase corticosterone and may confound studies of anxiety, while automated paradigms appear to distinguish themselves from stress. Chronic gentle handling studies should be interpreted with caution considering their known stress-induction as measured by corticosterone (Hairston et al., 2001). Future research should continue to explore the impact of DSD on anxiety-like behavior. It is imperative to screen for immediate and long-term changes in corticosterone as a first pass measure of stress. Moreover, a growing body of literature suggests there are sex-specific ASD-like phenotypes which may have previously been masked in females and warrant more detailed study (Wood-Downie et al., 2021).

4. Neural consequences of developmental sleep disruption

Neurodevelopmental disorders, including ASD, are associated with specific neuropathological hallmarks, which include changes in dendritic spine density and in the balance of excitation to inhibition (E/I) across various brain regions. Overgrowth of dendritic spines and lack of inhibition in local circuits are thought to contribute to the social deficits and rigid, stereotyped behaviors seen in children with autism (Kim et al., 2016). Sleep plays a major role in developmental brain patterning of circuits, and sleep deprivation results in both impaired pruning of dendritic spines and changes in E/I balance (Li et al., 2017).Children with autism often manifest profound sleep disturbances beginning early in life (Veatch et al., 2017). We and others have hypothesized that sleep disruption in autism directly contributes to neuropathological hallmarks of these neurodevelopmental disorders and clinical development. Rodent studies provide the valuable opportunity to experimentally manipulate sleep at various timepoints thereby establishing causality and can elucidate the neural mechanisms underlying behavioral dysfunction related to sleep disruption.

4.1. Spine maintenance and elimination, neuronal structure and mTOR

Changes in spine density are the most overlapping finding in developmental sleep disruption paradigms. Normal sleep functions to modulate spine density as evidenced by acute disruption paradigms and alterations have been seen in post-mortem tissue of individuals with ASD (Nagai et al., 2021; de Vivo and Bellesi, 2019; de Vivo et al., 2016; Bellesi et al., 2015; Hutsler and Zhang, 2010). It is plausible that prolonged disrupted sleep in development can modify and have persistent effects on cellular composition. Functionally, dendritic spines predominantly support excitatory neurotransmission, and their relative maturity can be inferred from their morphology (Hering and Sheng, 2001). An important consideration when comparing spine density findings between studies is the developmental trajectory of a given brain region. The timepoint of sleep disruption paradigm, and whether it overlaps with the ordinary maturation timeline impacts the likelihood that it will alter a given region. For instance, the rodent mPFC is a late-maturing brain region, sensitive to experience over a wide post-natal period (for review (Klune et al., 2021)) while visual cortex has a finite critical period (for review (Hensch, 2005)). In the ELSD method in prairie voles, there is increased spine density in the prelimbic region of layer 2/3 PFC in adulthood, specifically immature spines, pointing toward persistent effects of early-life sleep loss on late maturing cellular structures (Jones et al., 2021). Tissue from this study was examined in adulthood (P77-80) and there was no difference in density in deeper L5 of prelimbic or L2/3 and L5 infralimbic regions. Along with this increase in immature spines, is a reduction of vesicular glutamate transporter 1 (vGLUT1)-labelled terminals in both presynaptic and spine areas in ELSD voles, highlighting dysfunction in cortico-cortical communication. In the PFC of male rats at P33 and P90, Atrooz and colleagues found sweeping bar manipulation between P19-32 reduced GluA1 (AMPA receptor subunit) and GluN2b (NMDA receptor subunit) (Atrooz et al., 2019). However, because levels were assessed with western blotting, there is no layer specificity. Postsynaptic density protein (PSD95) was also reduced in sleep disrupted rats at P33 and P90. Reduced synaptic components in these models points to extensive neurotransmission dysfunction at the cellular level. P35-42 sleep-disruption in mice had no effect on spine

density in VTA dopamine projecting neurons in the mPFC (Bian et al., 2022). Early-life light advances produced lower branching order of pyramidal dendrites in the mPFC and dHPC, with a concomitant reduced length of dendrites in P90-110 animals (Ameen et al., 2022). Branching order and dendritic lengths are proxies for complexity of morphology, or maturity (Coleman and Riesen, 1968). Developmental IH from P10–P24 decreased branching of dendrites in L5 of PFC in 5-month old male rats (Kheirandish et al., 2005). Unlike previous studies, this is the oldest timepoint when dendritic branching was assessed, perhaps making the finding unique. 6–8 week old *Bmal1* KO mice showed increased Purkinje cell density in the cerebellum accompanied by spine density increases, specific to immature spines (Liu et al., 2022). Although in different regions and models, it is noteworthy, like Jones and colleagues, the increased spine density appeared specific to immature spines. Developmental sleep disruption can modify neuronal complexity and neuron to neuron communication by increasing dendritic spine density and reducing synaptic components. These outcomes appear to span multiple methods of disruption, with the strongest impact in protocols occurring in the first five weeks of life.

Neuronal composition can provide additional evidence for the molecular mechanisms underlying developmental sleep disruption. Early studies of REM deprivation using a non-specific chlorimipramine treatment found reduced overall volume of the cerebral cortex in adult rats, a crude measure of potential neuronal cell loss (Mirmiran et al., 1983). Regional expression of myelin basic protein (MBP) which contributes to the myelination of axons as assessed with western blotting is reduced in the striatum of *Fmr1* KO male mice at P94 who underwent gentle handling from P5-52 (Saré et al., 2022a). Chronic (4 days) sleep restriction increased metabolic and energy demand of mitochondria and endosomes within pyramidal cells of 1-month old mice (de Vivo et al., 2016).

One potential mechanism for how synapses are disrupted by DSD may be through alterations in the mammalian target of rapamycin (mTor) pathway. The mTOR pathway is a ubiquitous regulator of synaptic protein synthesis and is implicated in several neurodevelopmental disorders (Pagani et al., 2021). Chronic gentle handling from P5-52 increased expression of phosphorylated ribosomal protein 6 (p-S6) 235/6 and 240/4 in various brain regions of adult mice which represents downstream mTOR activity (Saré et al., 2019). Among its many functions, mTOR degrades the core clock gene *Bmal1*, and upregulated mTOR in tuberous sclerosis complex (TSC) mice leads to heightened *Bmal1* levels (Lipton et al., 2017). Naturally, in the *Bmal1* KO model, there are increased levels of mTORC1 – S6K1, which can be normalized with metformin treatment (Liu et al., 2022). This implies that neurodevelopmental changes related to mTOR hyperactivity may further alter circadian phenotypes. One major consideration for these profiles of mTOR activity is that they come from bulk tissue in each brain region, which reduces the sensitivity of the finding as compared to single cell comparison. mTOR pathway dysfunction is a plausible route of investigation considering the abundance of spine density changes reported because of sleep disruption.

4.2. Network activity, E/I balance and synaptic plasticity

Network activity generated by specific cell types – excitatory, inhibitory and interneurons is also susceptible to sleep loss in development. Excitatory-inhibitory (E/I) balance in the cortex is modulated by sleep-wake state, and dependent on Parvalbumin (PV)+ interneurons, which are most active during REM sleep (Niethard et al., 2016; Kuchibhotla et al., 2017). Modern *in-vivo* techniques allow for a precise measurement of cellular activity. Using *in-vivo* fiber photometry, Bian and colleagues demonstrate adolescent sleep loss in mice generates hypoactivity of dopaminergic cells in the ventral tegmental area (VTA) during novel social interaction and hyperactivity in the nucleus accumbens (NAc) during social interaction, neither change with subsequent bouts of interaction at P56 (Bian et al., 2022). Whole cell-patch clamp of the VTA cells shows increased membrane resistance. Careful tracing of this circuit reveals that sleep disruption during a critical period generates excess projections originating from the VTA onto medium spiny neurons in the NAc and diminished innervation of VTA to pyramidal neurons in the mPFC. Further experiments show that social novelty preference depends on activity of dopaminergic VTA cells, when activated with Designer Receptors Exclusively Activated by Designer Drugs (DREADDs), abolishing the behavior and when silenced, promoting the behavior. In the *Bmal1* KO model, there was an increased density of Purkinjie cells in the cerebellum and their spontaneous spiking rate was lower in 6–8 week old mice (Liu et al., 2022). Cell-attached electrophysiological recordings of cerebellar Purkinje cells showed reduced sEPSC amplitude and increased sIPSC pointing to overall cerebellar network dysfunction.

E/I balance, and network activity can be assessed indirectly in post-mortem tissue with the use of immunohistochemistry. DSD in prairie voles using cage disruption leads to multiple derangements that highlight altered E/I balance. Increased PV-interneurons in the somatosensory cortex were observed in prairie voles after DSD, suggesting increased inhibitory inputs in this region at P100 (Feng et al., 2000). Reduced vGlut1expression in prelimbic cortex indicate early life sleep impacts excitatory synaptic transmission at P80 (Jones et al., 2021). ELSD prairie voles show neuronal hyper-activity in the central and lateral amygdala following footshock via increased cfos immunoreactivity (Jones et al., 2021). Gentle handling of 6 week old mice for 8-days increased cfos expression in the prelimbic and infralimbic regions in males and female, though the specific cell-type is unknown (Murack et al., 2021). Following the hot-plate test, mice who underwent sleep disruption showed reduced cfos immunoreactivity, indicating neuronal hypo-activity in the periaqueductal grey, which was independent of any change in cortical thickness of the somatosensory cortex (Araujo et al., 2018). DSD in multiple modalities creates dysfunctional circuits.

Long-term potentiation (LTP) and long-term depression (LTD) are distinct measures of synaptic plasticity. Five to 8 week old rats deprived of REM sleep for 7–10 days were more likely to show LTP in response to low frequency stimulation applied to white matter fibers in the visual cortex instead of LTD, indicating a failure to produce inhibitory tone (Shaffery et al., 2006). REM sleep disruption in 1-month old rats extends the expression of LTP in the visual cortex (Shaffery et al., 2002). LTP is present beyond when it is expected developmentally, suggesting the role of sleep in expression of synaptic plasticity. Proper inhibitory tone is responsible for closing of critical periods, rearing in complete darkness abolishes the developmental reduction in LTP in 5-week old rats (Kirkwood et al., 1995). In this issue, two-photon imaging of excitatory neurons in primary visual cortex of 3-week old mice that underwent monocular-deprivation shows that REM sleep disruption leads to increased cortical firing to the deprived eye, disrupting ODP (Renouard et al., 2022). Levels of calcium/calmodulin kinase II (CaMKII), a recognized marker of synaptic plasticity was reduced in the PFC of P33 and P90 male rats who were sleep-disrupted between P19-32 (Atrooz et al., 2019).

DSD also impacts neurotransmitter receptor density and the concentration of neuromodulators. Chronic gentle handling reduces the number of 5-HT_{1A} expressing cells in the anterior cingulate cortex (ACC) and infralimbic cortex of 6 week old male and female mice (Murack et al., 2021). Shaffery et al. found multiple platforms over water in rats between P28-35 increased the concentration of thyrotropin-releasing hormone in the hypothalamus (Shaffery et al., 2002). Early life sleep loss can have persistent consequences on the neurobiological makeup of the brain. Developmental IH from P10-24 in rats increased norepinephrine in the mPFC of 5-month old males and females compared to controls (Kheirandish et al., 2005). Yang and colleagues found gentle handling in male rats reduced 5-HT and dopamine in the hypothalamus, reduced 5-HT and norepinephrine in the midbrain, reduced dopamine in the striatum and increased norepinephrine in the brainsteam in P36 rats (Yang et al., 2012). Melatonin production and normal pineal gland

activity is suppressed three-months after developmental sleep disruption between P21–P25 in rats (Chen et al., 2015). Though no other studies evaluated melatonin biosynthesis, there is evidence of melatonin deficiency among laboratory mice (Kasahara et al., 2010), making comparisons between species difficult. Neurotransmitter deficits may provide additional insight into behavioral and sleep/wake disruption.

Although neural mechanisms underlying developmental sleep disruption are less diverse than the behavioral phenotypes, it is clear DSD modifies normal network activity and cellular composition. When available, future studies should incorporate *in-vivo* cellular recordings which are paramount in identifying putative cell populations underlying disrupted behavior.

5. Conclusions and future directions

Early life sleep provides the foundation for typical neural development, while sleep disruption during sensitive developmental periods impact normal brain development and behavior, often persisting into adulthood. Rodent models of DSD provide an important approach with which to explore the function of sleep in shaping socio-emotional development. In this scoping review, we synthesized findings from 32 original research studies in rodent models of DSD across varied time points and methods.

It is apparent that the consequences of DSD differ depending on the specific developmental window and paradigm tested, highlighting the fact that not all DSD paradigms are equivalent. For example, impaired sociability was seen in mutant *Bmal1* mouse models, prairie voles with DSD from P14-21, and *Shank3*$^{\Delta C}$ mice with DSD, whereas methods that manipulated animals directly did not impair sociability. Social preference for a novel conspecific was impaired in DSD mice at P35-42 and heterozygous *Bmal1* mice, but in the socially monogamous prairie vole, DSD impaired social preference for the familiar conspecific (e.g. the partner). Compared to animal disruption, cage manipulation studies were less likely to impact corticosterone levels, developmental weight or find anxiety or depressive-like behavior, suggesting that interaction with the experimenter may complicate interpretation of a study. These studies highlight nuances in DSD effects on behavior and the species-typical nature of the effect.

To date, the neural mechanisms of DSD demonstrate widespread deficits in neurotransmission at the level of the synapse and circuit, creating dysfunctional behavior. For example, both DSD mice and DSD rats showed impaired ocular dominance plasticity and LTD expression at 1 month of age, indicating a robust deficit in synaptic plasticity across species. Several regions sensitive to DSD related to impaired behavior have been identified, including VTA (e.g., social novelty in mice), BLA (e.g., extinction of cued fear in voles), mPFC (sensorimotor/pain and partner preference in voles) and hippocampus (spatial working memory in mice and rats), highlighting the widespread nature of DSD effects across the brain. At the cellular level, a common theme that consistently emerged across DSD studies was increased dendritic spine density and reduced synaptic components, the essential structural components underlying proper cellular transmission. These findings closely parallel the hallmark pathology of neurodevelopmental disorders in humans, suggesting that DSD may be a causal or exacerbating factor in disease pathogenesis. Some pathways do not overlap, potentially providing novel insights while also relating to the infancy of the field in establishing the molecular mechanisms of DSD.

In conclusion, DSD in rodents can be a powerful tool with which to reveal both the biological function of sleep and the neural mechanisms underlying neurodevelopmental disorders. Given that methods differ, and reproducibility may be challenging across labs, gold standard EEG/EMG validation of DSD is important to ensure the paradigm used is specifically impacting sleep, and not simply rest-activity rhythms or locomotion. Identification of how different stages of sleep are impacted and whether animals acclimate to disruption will provide useful information in pursuit of mechanism. Verification of the stress effects of a manipulation through corticosterone or weight-trajectory can ensure the study does not unknowingly assay another condition (e.g. early life stress). It would be useful for models to incorporate multiple timepoints wherever possible to parse out the relative contribution of developmental sleep on their behavioral or neuropathological outcome of interest. Future work in genetic models could explore how mutations modify early-life sleep phenotypes more thoroughly. Finally, it is important to investigate both sexes in DSD studies, more than half of the studies discussed here came from exclusively male animals. Males and females may have different windows of vulnerability to DSD as well as in the specific neurodevelopmental disorder of interest. Sleep studies across three laboratory rodent species at unique developmental timepoints suggest that DSD has manifold effects on behavioral function and overlapping neural mechanisms, indicating DSD may play a causal role in the pathogenesis of neurodevelopmental disorders.

Declaration of competing interest

NEPM, CET, RMR and MML report no conflicts of interest.

Data availability

No data was used for the research described in the article.

Acknowledgements

This work was supported by a NIH T32 AG055378 to N.E.P.M, who is an ARCS Foundation Scholar. National Science Foundation NCS Foundation Award #1926818 to M.M.L. We thank Rikki Laser for illustrations of prairie voles. We thank Dr. David Jacobs and Randall Olson for valuable feedback. The graphical abstract and Fig. 1 were created using BioRender.com.

References

Adler, A., et al., 2021. Sleep Promotes the Formation of Dendritic Filopodia and Spines Near Learning-Inactive Existing Spines, vol. 118.
Ameen, R.W., Warshawski, A., Fu, L., Antle, M.C., 2022. Early life circadian rhythm disruption in mice alters brain and behavior in adulthood. Sci. Rep. 12, 7366.
Anders, T.F., Iosif, A.M., Schwichtenberg, A.J., Tang, K., Goodlin-Jones, B.L., 2011. Six-month sleep-wake organization and stability in preschool-age children with autism, developmental delay, and typical development. Behav. Sleep Med. 9, 92–106.
Anders, T., Iosif, A.M., Schwichtenberg, A.J., Tang, K., Goodlin-Jones, B., 2012. Sleep and daytime functioning: a short-term longitudinal study of three preschool-age comparison groups. Am. J. Intellect. Dev. Disabil. 117, 275–290.
Angoa-Pérez, M., Kane, M.J., Briggs, D.I., Francescutti, D.M., Kuhn, D.M., 2013. Marble burying and nestlet shredding as tests of repetitive, compulsive-like behaviors in mice. JoVE 50978. https://doi.org/10.3791/50978.
Arakawa, H., 2020. From multisensory assessment to functional interpretation of social behavioral phenotype in transgenic mouse models for autism spectrum disorders. Front. Psychiatr. 11.
Araujo, et al., 2018. Animal study neonatal sleep restriction increases nociceptive sensitivity in adolescent mice. Pain Physician 21, 137–148.
Arditi-Babchuk, H., Feldman, R., Eidelman, A.I., 2009. Rapid eye movement (REM) in premature neonates and developmental outcome at 6 months. Infant Behav. Dev. 32, 27–32.
Atrooz, F., Liu, H., Kochi, C., Salim, S., 2019. Early life sleep deprivation: role of oxido-inflammatory processes. Neuroscience 406, 22–37.
Atrooz, F., Alrousan, G., Hassan, A., Salim, S., 2022. Early-life sleep deprivation enhanced alcohol consumption in adolescent rats. Front. Neurosci. 16.
Beery, A.K., 2021. Familiarity and mate preference assessment with the partner preference test. Curr Protoc 1, e173.
Beery, A.K., Lopez, S.A., Blandino, K.L., Lee, N.S., Bourdon, N.S., 2021. Social selectivity and social motivation in voles. Elife. https://doi.org/10.7554/eLife.
Bellesi, M., de Vivo, L., Tononi, G., Cirelli, C., 2015. Effects of sleep and wake on astrocytes: clues from molecular and ultrastructural studies. BMC Biol. 13.
Bian, W.-J., Brewer, C.L., Kauer, J.A., de Lecea, L., 2022. Adolescent sleep shapes social novelty preference in mice. Nat. Neurosci. https://doi.org/10.1038/s41593-022-01076-8.
Blumberg, M.S., Sokoloff, G., 2001. Do infant rats cry? Psychol. Rev. 108, 83–95.
Blumberg, M.S., H Seelke, A.M., Lowen, S.B., Karlsson, K.A., Eugene Stanley, H., 2004. Dynamics of sleep-wake cyclicity in developing rats. Proc. Natl. Acad. Sci. USA 101.
Blumberg, M.S., Dooley, J.C., Sokoloff, G., 2020. The developing brain revealed during sleep. Curr Opin Physiol 15, 14–22.

Blumberg, M.S., Dooley, J.C., Tiriac, A., 2022. Sleep, plasticity, and sensory neurodevelopment. Neuron. https://doi.org/10.1016/j.neuron.2022.08.005.
Buchmann, A., et al., 2011. EEG sleep slow-wave activity as a mirror of cortical maturation. Cerebr. Cortex 21, 607–615.
Buckley, A.W., et al., 2010. Rapid eye movement sleep percentage in children with autism compared with children with developmental delay and typical development. Arch. Pediatr. Adolesc. Med. 164, 1032–1037.
Cao, J., Herman, A.B., West, G.B., Poe, G., Savage, V.M., 2020. Unraveling why we sleep: quantitative analysis reveals abrupt transition from neural reorganization to repair in early development. Sci. Adv. 6, 398–416.
Carola, V., Olimpio, F.D.', Brunamonti, E., Mangia, F., Renzi, P., 2002. Evaluation of the elevated plus-maze and open-field tests for the assessment of anxiety-related behaviour in inbred mice. Behav. Brain Res. 134, 49–57.
Changeux, J.-P., Danchin, A., 1976. Selective stabilisation of developing synapses as a mechanism for the specification of neuronal networks. Nature 264.
Chen, L.Y., et al., 2015. Early-life sleep deprivation persistently depresses melatonin production and bio-energetics of the pineal gland: potential implications for the development of metabolic deficiency. Brain Struct. Funct. 220, 663–676.
Christopher Ehlen, J., et al., 2017. Bmal1 function in skeletal muscle regulates sleep. Elife 26557.
Cohen, S.J., Stackman, R.W., 2015. Assessing rodent hippocampal involvement in the novel object recognition task. A review. Behav. Brain Res. 285, 105–117.
Coleman, P.D., Riesen, A.H., 1968. Environmental effects on cortical dendritic fields I. Rearing in the dark. J. Anat. 102, 363–374.
Colrain, I.M., Baker, F.C., 2011. Changes in sleep as a function of adolescent development. Neuropsychol. Rev. 21, 5–21.
da Silva Rocha-Lopes, J., Machado, R.B., Suchecki, D., 2018. Chronic REM sleep restriction in juvenile male rats induces anxiety-like behavior and alters monoamine systems in the amygdala and Hippocampus. Mol. Neurobiol. 55, 2884–2896.
de Vivo, L., Bellesi, M., 2019. The role of sleep and wakefulness in myelin plasticity. Glia 67, 2142–2152.
de Vivo, L., et al., 2016. Loss of sleep affects the ultrastructure of pyramidal neurons in the adolescent mouse frontal cortex. Sleep 39, 861–874.
de Vivo, L., et al., 2017. Ultrastructural evidence for synaptic scaling across the wake/sleep cycle. Science 355, 507–510, 1979.
de Vivo, L., et al., 2019. Evidence for sleep-dependent synaptic renormalization in mouse pups. Sleep 42.
del Rio-Bermudez, C., Kim, J., Sokoloff, G., Blumberg, M.S., 2020. Active sleep promotes coherent oscillatory activity in the cortico-hippocampal system of infant rats. Cerebr. Cortex 30, 2070–2082.
Díaz-Román, A., Zhang, J., Delorme, R., Beggiato, A., Cortese, S., 2018. Sleep in youth with autism spectrum disorders: systematic review and meta-analysis of subjective and objective studies. Evid. Base Ment. Health 21, 146–154.
Diering, G.H., et al., 2017. Homer1a drives homeostatic scaling-down of excitatory synapses during sleep. Science 1979, 511–515.
Dooley, J.C., Blumberg, M.S., 2018. Developmental 'awakening' of primary motor cortex to the sensory consequences of movement. Elife. https://doi.org/10.7554/eLife.41841.001.
Feinberg, I., Campbell, I.G., 2013. Longitudinal sleep EEG trajectories indicate complex patterns of adolescent brain maturation. Am. J. Physiol. Regul. Integr. Comp. Physiol. 304.
Feng, P., Ma, Y., 2003. Instrumental REM sleep deprivation in neonates leads to adult depression-like behaviors in rats. Sleep 26.
Feng, P., Vogel, G., Obermeyer, W., Kinney, G., 2000. An instrumental method for long-term continuous REMSleep deprivation of neonatal rats. Sleep 23.
Feng, P., Ma, Y., Vogel, G., 2001. Ontogeny of REM rebound in postnatal rats. Sleep 24, 645–653.
Frank, M.G., Morrissette, R., Heller, A.H.C., Craig, H., 1998. Effects of sleep deprivation in neonatal rats. Am. J. Physiol. 275, R148–R157.
Frank, M.G., Issa, N.P., Stryker, M.P., Keck, W.M., 2001. Sleep enhances plasticity in the developing visual cortex. Neuron 30.
Gertner, S., et al., 2002. Sleep-wake patterns in preterm infants and 6 month's home environment: implications for early cognitive development. Early Hum. Dev. 68, 93–102.
Gómez, L.J., Dooley, J.C., Sokoloff, G., Blumberg, M.S., 2021. Parallel and serial sensory processing in developing primary somatosensory and motor cortex. J. Neurosci. 41, 3418–3431.
Gómez, L.J., Dooley, J.C., Blumberg, M.S., 2022. Activity in developing prefrontal cortex is shaped by sleep and sensory experience. bioRxiv. https://doi.org/10.1101/2022.07.31.502200.
Hadaya, L., et al., 2022. Distinct neurodevelopmental trajectories in groups of very preterm children screening positively for autism spectrum conditions. J. Autism Dev. Disord. https://doi.org/10.1007/s10803-022-05789-4.
Hairston, I.S., et al., 2001. Sleep deprivation elevates plasma corticosterone levels in neonatal rats. Neurosci. Lett. 315, 29–32.
Heavner, W.E., Smith, S.E.P., 2020. Resolving the synaptic versus developmental dichotomy of autism risk genes. Trends Neurosci. 43 227–241. https://doi.org/10.1016/j.tins.2020.01.009. Preprint at.
Hensch, T.K., 2005. Critical period plasticity in local cortical circuits. Nat. Rev. Neurosci. 6, 877–888.
Hering, H., Sheng, M., 2001. Dendritic Spines: Structure, Dynamics and Regulation.
Hutsler, J.J., Zhang, H., 2010. Increased dendritic spine densities on cortical projection neurons in autism spectrum disorders. Brain Res. 1309, 83–94.
Jahrami, H.A., et al., 2022. Sleep disturbances during the COVID-19 pandemic: a systematic review, meta-analysis, and meta-regression. Sleep Med. Rev. 62.
Jones, C.E., et al., 2019a. Early-life sleep disruption increases parvalbumin in primary somatosensory cortex and impairs social bonding in prairie voles. Sci. Adv. 5.
Jones, C.E., Navis, T.M., Teutsch, P., Opel, R.A., Lim, M.M., 2019b. Acoustic prepulse inhibition in male and female prairie voles: implications for models of neuropsychiatric illness. Behav. Brain Res. 360, 298–302.
Jones, C.E., Wickham, P.T., Lim, M.M., 2020. Early life sleep disruption is a risk factor for increased ethanol drinking after acute footshock stress in prairie voles. Behav. Neurosci. 134, 424–434.
Jones, C.E., et al., 2021. Early life sleep disruption alters glutamate and dendritic spines in prefrontal cortex and impairs cognitive flexibility in prairie voles. Current Research in Neurobiology 2, 100020.
Kaidanovich-Beilin, O., Lipina, T., Vukobradovic, I., Roder, J., Woodgett, J.R., 2010. Assessment of social interaction behaviors. JoVE. https://doi.org/10.3791/2473.
Kasahara, T., Abe, K., Mekada, K., Yoshiki, A., Kato, T., 2010. Genetic variation of melatonin productivity in laboratory mice under domestication. Proc. Natl. Acad. Sci. U. S. A. 107, 6412–6417.
Kheirandish, L., Gozal, D., Pequignot, J.M., Pequignot, J., Row, B.W., 2005. Intermittent hypoxia during development induces long-term alterations in spatial working memory, monoamines, and dendritic branching in rat frontal cortex. Pediatr. Res. 58, 594–599.
Kim, H., Lim, C.S., Kaang, B.K., 2016. Neuronal mechanisms and circuits underlying repetitive behaviors in mouse models of autism spectrum disorder. Behav. Brain Funct. 12.
Kirkwood, A., Hey-Kyoung, L., Bear, M., 1995. Co-regulation of long-term potentiation and experience dependent synaptic plasticity in visual cortex by age and experience. Nature 375, 328–331.
Klavir, O., Prigge, M., Sarel, A., Paz, R., Yizhar, O., 2017. Manipulating fear associations via optogenetic modulation of amygdala inputs to prefrontal cortex. Nat. Neurosci. 20, 836–844.
Klune, C.B., Jin, B., Denardo, L.A., 2021. Linking mpfc circuit maturation to the developmental regulation of emotional memory and cognitive flexibility. Elife 10.
Krüttner, S., et al., 2022. Absence of familiarity triggers hallmarks of autism in mouse model through aberrant tail-of-striatum and prelimbic cortex signaling. Neuron 110, 1468–1482 e5.
Kuchibhotla, K.v., et al., 2017. Parallel processing by cortical inhibition enables context-dependent behavior. Nat. Neurosci. 20, 62–71.
Kurth, S., et al., 2017. Traveling slow oscillations during sleep: a marker of brain connectivity in childhood. Sleep 40.
Li, W., Ma, L., Yang, G., Gan, W.B., 2017. REM sleep selectively prunes and maintains new synapses in development and learning. Nat. Neurosci. 20, 427–437.
Lipton, J.O., et al., 2017. Aberrant proteostasis of BMAL1 underlies circadian abnormalities in a paradigmatic mTOR-opathy. Cell Rep. 20, 868–880.
Liu, D., et al., 2022. Autistic-like behavior and cerebellar dysfunction in Bmal1 mutant mice ameliorated by mTORC1 inhibition. Mol. Psychiatr. https://doi.org/10.1038/s41380-022-01499-6.
Lord, C., Elsabbagh, M., Baird, G., Veenstra-Vanderweele, J., 2018. Autism spectrum disorder. Lancet 392, 508–520.
Lord, J.S., et al., 2022. Early life sleep disruption potentiates lasting sex-specific changes in behavior in genetically vulnerable Shank3 heterozygous autism model mice. Mol. Autism. 13.
Lorsung, E., Karthikeyan, R., Cao, R., 2021. Biological timing and neurodevelopmental disorders: a role for circadian dysfunction in autism spectrum disorders. Front. Neurosci. 15.
Lu, H.C., Pollack, H., Lefante, J.J., Mills, A.A., Tian, D., 2019. Altered sleep architecture, rapid eye movement sleep, and neural oscillation in a mouse model of human chromosome 16p11.2 microdeletion. Sleep 42.
MacDuffie, K.E., et al., 2020. Sleep problems and trajectories of restricted and repetitive behaviors in children with neurodevelopmental disabilities. J. Autism Dev. Disord. 50, 3844–3856.
Machado, R.B., Tufik, S., Suchecki, D., 2013. Role of corticosterone on sleep homeostasis induced by REM sleep deprivation in rats. PLoS One 8.
Marcano-Reik, A.J., Prasad, T., Weiner, J.A., Blumberg, M.S., 2010. An abrupt developmental shift in callosal modulation of sleep-related spindle bursts coincides with the emergence of excitatory-inhibitory balance and a reduction of somatosensory cortical plasticity. Behav. Neurosci. 124, 600–611.
Martínez-Cayuelas, E., et al., 2022. Sleep problems and circadian functioning in children and adolescents with autism spectrum disorder. Pediatr. Neurol. 126, 57–64.
Mason, G.M., Lokhandwala, S., Riggins, T., Spencer, R.M.C., 2021. Sleep and human cognitive development. Sleep Med. Rev. 57.
Medina, E., et al., 2022. Shank3 influences mammalian sleep development. J. Neurosci. Res. 1–13. https://doi.org/10.1002/jnr.25119.
Michetti, C., Ricceri, L., Scattoni, M.L., 2012. Modeling social communication deficits in mouse models of autism, pp. 1–8. https://doi.org/10.4172/2165-7890.S1-007. Autism S1:007.
Mirmiran, M., 1995. The function of fetal/neonatal rapid eye movement sleep. Behav. Brain Res. 69, 13–22.
Mirmiran, M., van de Poll, N.E., Corner, M.A., van Oyen, H.G., Bour, H.L., 1981. Suppression of active sleep* by chronic treatment with chlorimipramine during early postnatal development: effects upon adult sleep and behavior in the rat. Brain Res. 204, 129.
Mirmiran, M., et al., 1983. Effects of experimental suppression of active (REM) sleep during early development upon adult brain and behavior in the rat. Dev. Brain Res. 7, 277–286.
Missig, G., McDougle, C.J., Carlezon, W.A., 2020. Sleep as a translationally-relevant endpoint in studies of autism spectrum disorder (ASD). Neuropsychopharmacology 45, 90–103.

Miyamoto, H., Katagiri, H., Hensch, T., 2003. Experience-dependent slow-wave sleep development. Nat. Neurosci. 6, 553–554.
Moy, S.S., et al., 2004. Sociability and preference for social novelty in five inbred strains: an approach to assess autistic-like behavior in mice. Gene Brain Behav. 3, 287–302.
Murack, M., et al., 2021. Chronic sleep disruption induces depression-like behavior in adolescent male and female mice and sensitization of the hypothalamic-pituitary-adrenal axis in adolescent female mice. Behav. Brain Res. 399.
Nagai, H., de Vivo, L., Marshall, W., Tononi, G., Cirelli, C., 2021. Effects of severe sleep disruption on the synaptic ultrastructure of young mice. eNeuro 8.
Nelson, A.B., Faraguna, U., Zoltan, J.T., Tononi, G., Cirelli, C., 2013. Sleep patterns and homeostatic mechanisms in adolescent mice. Brain Sci. 3, 318–343.
Niethard, N., et al., 2016. Sleep-stage-specific regulation of cortical excitation and inhibition. Curr. Biol. 26, 2739–2749.
Ohayon, M., Carskadon, M., Guilleminault, C., Vitiello, M., 2004. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep 27, 1256–1273.
Oliva, A., Fernández-Ruiz, A., Leroy, F., Siegelbaum, S.A., 2020. Hippocampal CA2 sharp-wave ripples reactivate and promote social memory. Nature 587, 264–269.
Orefice, L.L., 2020. Peripheral somatosensory neuron dysfunction: emerging roles in autism spectrum disorders. Neuroscience 445, 120–129.
Orefice, L.L.L., et al., 2016. Peripheral mechanosensory neuron dysfunction underlies tactile and behavioral deficits in mouse models of ASDs. Cell 166, 299–313.
Owens, J., et al., 2014. Insufficient sleep in adolescents and young adults: an update on causes and consequences. Pediatrics 134, e921–e932.
Paavonen, E.J., et al., 2020. Normal sleep development in infants: findings from two large birth cohorts. Sleep Med. 69, 145–154.
Pagani, M., et al., 2021. mTOR-related synaptic pathology causes autism spectrum disorder-associated functional hyperconnectivity. Nat. Commun. 12.
Reeb-Sutherland, B.C., et al., 2011. One-month-old human infants learn about the social world while they sleep. Dev. Sci. 14, 1134–1141.
Renouard, L., et al., 2022. REM sleep promotes bidirectional plasticity in developing visual cortex in vivo. Neurobiol Sleep Circadian Rhythms 12.
Rensing, N., Moy, B., Friedman, J.L., Galindo, R., Wong, M., 2018. Longitudinal analysis of developmental changes in electroencephalography patterns and sleep-wake states of the neonatal mouse. PLoS One 13.
Ribeiro, S., Goyal, V., Mello, C. v, Pavlides, C., 1999. Brain Gene Expression during REM Sleep Depends on Prior Waking Experience.
Roffwarg, H.P., Muzio, J.N., Dement, W.C., 1966. Ontogenetic development of the human sleep-dream cycle. Science 152, 604–619, 1979.
Row, B., Kheirandish, L., Neville, J., Gozal, D., 2002. Impaired spatial learning and hyperactivity in developing rats exposed to intermittent hypoxia. Pediatr. Res. 52, 449–453.
Saré, R.M., Levine, M., Hildreth, C., Picchioni, D., Smith, C.B., 2016. Chronic sleep restriction during development can lead to long-lasting behavioral effects. Physiol. Behav. 155, 208–217.
Saré, R.M., et al., 2017. Deficient sleep in mouse models of fragile X syndrome. Front. Mol. Neurosci. 10.
Saré, R.M., et al., 2019. Chronic sleep restriction in developing male mice results in long lasting behavior impairments. Front. Behav. Neurosci. 13.
Saré, R.M., et al., 2022a. Behavioral and molecular consequences of chronic sleep restriction during development in fragile X mice. Front. Neurosci. 16.
Saré, R.M., et al., 2022b. Behavioral and molecular consequences of chronic sleep restriction during development in fragile X mice. Front. Neurosci. 16.
Seelke, A.M.H., Blumberg, M.S., 2008. The microstructure of active and quiet sleep as cortical delta activity emerges in infant rats. Sleep 31.
Shaffery, J.P., Sinton, C.M., Bissette, G., Roffwarg, H.P., Marks, G.A., 2002. Rapid eye movement sleep deprivation modifies expression of long-term potentiation in visual cortex of immature rats. Neuroscience 110, 431–443.
Shaffery, J.P., Lopez, J., Bissette, G., Roffwarg, H.P., 2006. Rapid eye movement sleep deprivation in post-critical period, adolescent rats alters the balance between inhibitory and excitatory mechanisms in visual cortex. Neurosci. Lett. 393, 131–135.
Shellhaas, R.A., et al., 2022. Lateralized neonatal EEG coherence during sleep predicts language outcome. Pediatr. Res. 91, 962–969.
Singla, R., et al., 2022. Haploinsufficiency of a circadian clock gene Bmal1 (arntl or Mop3) causes brain-wide mTOR hyperactivation and autism-like behavioral phenotypes in mice. Int. J. Mol. Sci. 23, 6317.
Smarr, B.L., Grant, A.D., Perez, L., Zucker, I., Kriegsfeld, L.J., 2017. Maternal and early-life circadian disruption have long-lasting negative consequences on offspring development and adult behavior in mice. Sci. Rep. 7.
Spano, G.M., et al., 2019. Sleep deprivation by exposure to novel objects increases synapse density and axon-spine interface in the hippocampal ca1 region of adolescent mice. J. Neurosci. 39, 6613–6625.
Spear, L.P., 2000. The adolescent brain and age-related behavioral manifestations. Neurosci. Biobehav. Rev. 24, 417–463.
Tarokh, L., Carskadon, M.A., 2010. Developmental changes in the human sleep EEG during early adolescence. Sleep 33.
Tarokh, L., Saletin, J.M., Carskadon, M.A., 2016. Sleep in adolescence: physiology, cognition and mental health. Neurosci. Biobehav. Rev. 70, 182–188.
Tesler, N., Gerstenberg, M., Huber, R., 2013. Developmental changes in sleep and their relationships to psychiatric illnesses. Curr. Opin. Psychiatr. 26, 572–579.
Tononi, G., Cirelli, C., 2014. Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. Neuron 81, 12–34.
Veatch, O.J., et al., 2017. Shorter sleep duration is associated with social impairment and comorbidities in ASD. Autism Res. 10, 1221–1238.
Veatch, O.J., et al., 2021. Evaluating sleep disturbances in children with rare genetic neurodevelopmental syndromes. Pediatr. Neurol. 123, 30–37.
Verhoeff, M.E., et al., 2018. The bidirectional association between sleep problems and autism spectrum disorder: a population-based cohort study. Mol. Autism. 9.
Wallace, E., et al., 2015. Differential effects of duration of sleep fragmentation on spatial learning and synaptic plasticity in pubertal mice. Brain Res. 1615, 116–128.
Wang, B., et al., 2016. Developmental trajectories of sleep problems from childhood to adolescence both predict and are predicted by emotional and behavioral problems. Front. Psychol. 7.
Weisman, O., Magori-Cohen, R., Louzoun, Y., Eidelman, A.I., Feldman, R., 2011. Sleep-wake transitions in premature neonates predict early development. Pediatrics 128, 706–714.
Williams, J.R., Catania, K.C., Carter, C.S., 1992. Development of partner preferences in female prairie voles (Microtus ochrogaster): the role of social and sexual experience. Homones and Behavior 26, 339–349.
Wood-Downie, H., et al., 2021. Sex/gender differences in camouflaging in children and adolescents with autism. J. Autism Dev. Disord. 51, 1353–1364.
Yang, S.R., Sun, H., Huang, Z.L., Yao, M.H., Qu, W.M., 2012. Repeated sleep restriction in adolescent rats altered sleep patterns and impaired spatial learning/memory ability. Sleep 35, 849–859.
Zamore, Z., Veasey, S.C., 2022. Neural consequences of chronic sleep disruption. Trends Neurosci. https://doi.org/10.1016/j.tins.2022.05.007.
Zhou, Y., et al., 2020. REM sleep promotes experience-dependent dendritic spine elimination in the mouse cortex. Nat. Commun. 11.