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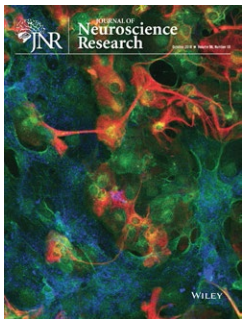
REVIEW



Sleep problems in Rett syndrome animal models: A systematic review

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Abstract

Due to the discovery of Rett Syndrome (RTT) genetic mutations, animal models have been developed. Sleep research in RTT animal models may unravel novel neural mechanisms for this severe neurodevelopmental heritable rare disease. In this systematic literature review we summarize the findings on sleep research of 13 studies in animal models of RTT. We found disturbed efficacy and continuity of sleep in all genetically mutated models of mice, cynomolgus monkeys, and *Drosophila*. Models presented highly fragmented sleep with distinct differences in 24-hr sleep/wake cyclicity and circadian arrhythmicity. Overall, animal models mimic sleep complaints reported in individuals with RTT. However, contrary to human studies, in mutant mice, attenuated sleep delta waves, and sleep apneas in non-rapid eye movement sleep were reported. Future studies may focus on sleep structure and EEG alterations, potential central mechanisms involved in sleep fragmentation and the occurrence of sleep apnea across different sleep stages. Given that locomotor dysfunction is characteristic of individuals with RTT, studies may consider to integrate its potential impact on the behavioral analysis of sleep.

KEYWORDS

circadian rhythm, *Drosophila*, monkey, mouse, Rett syndrome, sleep

1 | INTRODUCTION

Rett Syndrome (RTT, MIM 312750), a progressive neurodevelopmental disease, has an approximately incidence rate of 1 in 10,000 (Neul et al., 2010) in live female births. RTT becomes visible through a neurodevelopmental regression following 6 to 18 months apparent normal developmental period. Loss of acquired language skills, stereotypic hand movements, and comprehensive cognitive, social, motor skill impairments (Hagberg, Goutières, Hanefeld, Rett, & Wilson, 1985; Hagberg & Witt-Engerstrom, 1986; Kerr et al., 2001) are characteristics of the disease. In addition, typical and atypical variants have been defined, framing RTT when clinical features vary subtly (Neul et al., 2010).

Studies suggest that sleep problems such as night waking, night screaming, and night laughing (Boban, Leonard, Wong, Wilson, & Downs, 2018; Boban et al., 2016; Hagebeuk, van den Bossche, & de Weerd, 2013; Mangatt et al., 2016; Wong, Leonard, Jacoby, Ellaway, & Downs, 2015; Young et al., 2007) are prevalent in individuals with RTT, that is, night waking affects over 80% (Wong et al., 2015) and difficulty falling asleep has a prevalence rate of 60.4% (Boban et al., 2016). Impaired sleep structure and sleep breathing patterns have also been reported when applying polysomnography (PSG) and electroencephalogram (EEG) (Amaddeo et al., 2019; Ammanuel et al., 2015; Hagebeuk, Bijlmer, Koelman, & Poll-The, 2012; Hagebeuk, van den Bossche, & de Weerd, 2013; Marcus et al., 1994). Especially, the disorders of respiratory control when awake are well recognized and described in individuals with RTT (Julu et al., 2001; Lugaresi, Cirignotta, & Montagna, 1985; Tarquinio et al., 2018). Yet findings are inconsistent regarding respiratory disorders during sleep (d'Orsi, Demaio, Scarpelli, Calvario, & Minervini, 2009; Marcus

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et al., 1994). To date, there is limited knowledge about the mechanistic pathways of sleep problems in RTT.

Since Amir et al. (1999) discovered the mutations in methyl-CpG-binding protein 2 (*MECP2*) gene causing the loss-of-function alike RTT, which was primarily identified in sporadic cases of individuals with RTT (i.e., 94.2%) (Frullanti et al., 2019), substantial advances in animal modeling of RTT could be noticed. That is, *Mecp2* exons deletion mouse models (Chen, Akbarian, Tudor, & Jaenisch, 2001; Guy, Hendrich, Holmes, Martin, & Bird, 2001) were generated with around 6 weeks of age the onset of Rett-like symptoms. Later the animal models of rat (Patterson, Hawkins, Arps, Mulkey, & Olsen, 2016), *Drosophila* (Kudo et al., 2001), and cynomolgus monkey (Liu et al., 2016) were generated enlarging the potential of animal RTT research. Recently, genetic engineering tools like transcription activator-like effector nucleases (TALENs) (Liu et al., 2014) and regularly interspaced short palindromic repeats (CRISPR)/Cas-mediated system (Yang et al., 2013, Tsuchiya et al., 2015) were applied, allowing sequence-specific DNA-binding modules for RTT animal research and site-specific analysis. Although a large number of *MECP2* mutations are possible, of which a huge amount have been identified in individuals with RTT (Krishnaraj, Ho, & Christodoulou, 2017), some *MECP2* mutations possibly occur in other neurodevelopmental disorders (Couvert et al., 2001).

In addition to *MECP2* gene, other genetic mutations were linked with RTT variants, such as cyclin-dependent kinase like 5 (*CDKL5*) (Tao et al., 2004; Weaving et al., 2004) and forkhead box G1 (*FOXG1*) (Ariani et al., 2008), affecting respectively 3.2% and 2.6% of individuals with RTT (Frullanti et al., 2019). *CDKL5* for instance has been suggested to overlap pathogenic processes with *MECP2* (Mari et al., 2005). Several mutation-matched animal models have been generated subsequently (Amendola et al., 2014; Martynoga, Morrison, Price, & Mason, 2005). To date, the animal models have allowed combined investigations on the clinical features and cellular metabolism, providing unique insights into this syndrome. Certainly, not all clinical features can be mimicked by animal models, such as speech loss but several functions could be investigated (Lombardi, Baker, & Zoghbi, 2015).

Sleep and circadian clock rhythmicity are considered basic needs for species (Bhadra, Thakkar, Das, & Pal Bhadra, 2017; Pittendrigh, 1993). Sleep pressure and timing are determined by both homeostatic and circadian regulation. Biorhythms are synchronized by the environmental light–dark cycle pacemaker in suprachiasmatic nucleus (SCN), which times also the rhythms of behavior and metabolism (Rosenwasser & Turek, 2015). A circadian clock alike humans equally exists in animals, especially locomotion fluctuates in consistency with circadian rhythmicity (Johnston, Ordovás, Scheer, & Turek, 2016). While human beings are diurnal species, rodents are nocturnal creatures (Ripperger, Jud, & Albrecht, 2011), such that they sleep during luminous phase and are awake during darkness.

After brain electrical activity patterns (Caton & Disease, 1875; Schoenberg, 1974) and sleep cortical rhythms were discovered (Loomis, Harvey, & Hobart, 1935) the sleep–wake cycle has been vastly investigated (Aserinsky & Kleitman, 1953; Borbély, 1982; Jouvet, 1969; Siegel & Gordon, 1965). Namely, EEG technology facilitates translational research and in particular prospers animal sleep experiments. Scoring the cortical EEG signals (Brankack, Kukushka, Vyssotski, & Draguhn, 2010) allows classification of behavioral states into wakefulness, rapid eye movement (REM) sleep (i.e., wake-like EEG with rapid eye movements and muscle atonia interrupted by irregular twitches of limbs), and non-rapid eye movement (NREM) sleep (i.e., 12–15 Hz sleep spindles and widespread high amplitude low frequency delta wave of 0.5–4 Hz) (Cirelli & Tononi, 2015). In rodent experiments, NREM has sometimes been presented solely as slow wave sleep (SWS), that is, deepest NREM sleep stage characterized by widespread slow wave activity (SWA) of 0.25–4.0 Hz waves (Franken, Malafosse, & Tafti, 1998; Neckelmann & Ursin, 1993). Electromyogram (EMG) waveforms consolidated with EEG recordings ensure the reliability of sleep–wake states in animal studies. For instance, EEG/EMG recordings, involving locomotor activity monitoring by (infrared) detector/video defines "sleep" as complete inactivity for a period of several consecutive minutes (i.e., 1 min for rodent and 5 min for *Drosophila*) are widely used. Whereas whole-body plethysmography (WBP) could assess the sleep and breathing pattern simultaneously.

Thus, experiments involving genetically modified animal models combined with valid sleep measures may reproduce the clinical complaints reported in individuals with RTT, and reveal perturbed sleep mechanisms. Given the prevalent complaints of problematic sleeping in individuals with RTT such as night waking and difficulty falling asleep, a systematic review of RTT animal sleep research was performed. We aim to summarize sleep research findings in RTT animal models, improving our understanding of sleep abnormalities in RTT and their potential neural mechanisms.

Significance

Sleep complaints are prevalent but various in RTT. Animal models of RTT showed fragmented sleep in 24-hr cycles. Findings also suggest the absence of sleep rebound after poor sleep, indicating perturbed homeostatic and circadian regulation. More studies measuring electrocerebral activity and investigating rapid eye movement sleep are needed. Detailed examination of the disturbed sleep–wake cyclicity in RTT animal models may uncover critical areas in brain neuronal targets.

2 | METHODS

This systematic review was undertaken according to the PRISMA guidelines (Moher, Liberati, Tetzlaff, Altman, & Group, 2009) with no time limitation applied.

2.1 | Search strategy

We searched in five electronic databases: PubMed, Web of Science, PsycINFO, Ebsco, and Scopus, up till March 06, 2020 (Figure 1). The search strategy was designed to identify and collect animal studies investigating sleep in RTT models. The search terms used in PubMed were "((((((((((((((rett syndrome) OR syndrome, rett) OR autism-dementia-ataxia-loss of purposeful hand use syndrome) OR autism-dementia-ataxia-loss of purposeful hand use syndrome) OR (autism, dementia, ataxia, and loss of purposeful hand use)) OR rett disorder) OR rett's disorder) OR rett's syndrome) OR rett's syndrome) OR syndrome, rett's) OR cerebro atrophic hyperammonemia) OR cerebro atrophic hyperammonemia) OR hyperammonemia, cerebro atrophic) OR hyperammonemia, cerebro atrophic)) AND sleep," and search items used in other databases are listed in Supplement.

Screening of the title, abstract, and key words of publications was performed to select animal studies that fulfill the inclusion criteria. Next, full texts were obtained for final determination of inclusion or exclusion, and also their reference lists were checked simultaneously.

2.2 | Inclusion criteria

Sleep studies in RTT animal models involving observational experiments and interventions published in peer-reviewed journals were included. Our review focused on all RTT mutant models including variants of *Mecp2*, *Cdkl5*, and *Foxg1*. RTT mutant animal sleep data could be numerical, graphical, or a clear description allowing extraction of sleep information. In case of interventional studies only the baseline data were used.

2.3 | Exclusion criteria

Review papers, conference proceedings and thesis works were excluded. Studies reporting "sleep" but not presenting data were excluded.

2.4 | Data management and statistical analysis

The characteristics of included studies such as authors, country, year, and main findings on sleep were tabulated. Subgroups were formed based on the details of the methodology: type of animal model, respiratory dysfunction, behavior, and circadian rhythm. In case, calculations for descriptive analysis of mean, standard deviation (*SD*), median or sum were performed (Microsoft Excel), they will be reported accordingly.

3 | RESULTS

3.1 | Publication overview

Thirteen studies were identified by this systematic search as summarized in Table 1. We categorized the studies into three groups according to the species of animal used for modeling RTT, which were one on cynomolgus monkey (Y. Chen et al., 2017), two on

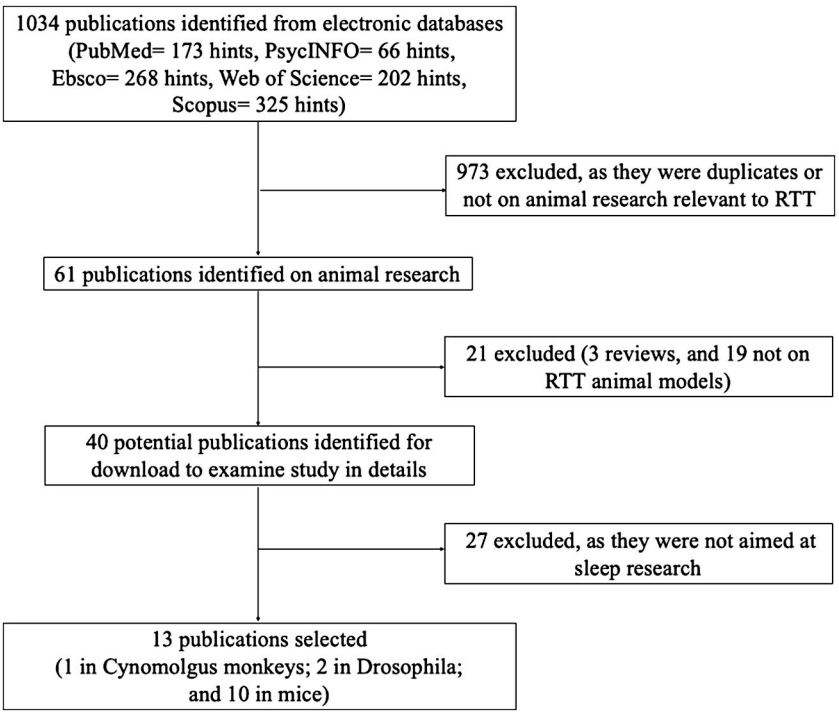

FIGURE 1 Flowchart of article selection up to date of March 06, 2020

TABLE 1 Summary information of selected publications

Author	Country	Study field	Animal species	Modeling method	Mutation information	Number of mutated animals in sleep measurement	Gender of mutated animals	Age/weight of mutated animals (mean ± *SD*) [range]	Conclusions
Fuchs et al. (2018)	Italy	Model building	C57BL/6N, C57BL/6J mice	*Cdkl5* null strain in the C57BL/6N background developed in and backcrossed in C57BL/6J for three generations	*Cdkl5* KO (+/−) *Cdkl5* KO (−/−)	11 8	F	14 weeks	$Cdkl5^{+/-}$ and $Cdkl5^{-/-}$ had more frequent sleep apneas during NREM sleep
Chen et al. (2017)	China	Model building	Cynomolgus monkeys	TALENs injection of *MECP2*-targeted offer into zygotes	*Mecp2* deficient (Multiple mutations on *Mecp2* exon 3)	5	F		Monkey models showed fragmented sleep
Lo Martire et al. (2017)	Italy	Sleep apneas	C57BL/6J mice		*Cdkl5*-KO (−/y)	10	M	(15.9 ± 0.9 weeks)/ (25.5 ± 0.2gr)	Sleep apneas are a core feature of CDKL5 disorder
Gupta et al. (2016)	United States	Sleep behavior	*Drosophila*		$T\beta h^{M18}$ *tdc2-gal4 UAS-hMeCP2* $^{FL,\ R294X,\ R106W,\ \Delta166}$ (truncating mutation, missense mutation)	21–50	M	[2–3 days and after]	hMeCP2 expression in *Drosophila* resulted in phase-specific sleep loss and sleep fragmentation
Tsuchiya et al. (2015)	Japan	Circadian rhythm	C57BL/6J mice	The fertilized eggs were injected with a mixture of Cas9 mRNA and sgRNA expression plasmid	*Mecp2*-deficient $PER2^{Luciferase}$ knock-in (mutation in exon 3)	4	F and M	[4 weeks and after]	*Mecp2* deficiency abrogates the circadian pacemaking ability of the SCN
Li et al. (2015)	United States	Circadian rhythm	C57BL/6J mice	$Mecp2^{-/+}$ female mutants crossed to male mice hemizygotes inserted endogenous *Period2* gene	$Mecp2^{tm1.1Jae}$/Mmucd (delete exon 3)	8	M	[7–8 weeks]	MeCP2 mutant mice were vulnerable to circadian disruption as chronic jet lag accelerated mortality
Hess-Homeier et al. (2014)	United States	Sleep behavior	*Drosophila*		*alrm-Gal4/ UAS-hMeCP2*^{FL}	30	M	[3–5 days and after]	hMeCP2 expression reduced sleep levels, altered daytime/nighttime sleep patterns, and generated sleep maintenance deficits
Johnston et al. (2014)	United States	EEG	C57BL/6 mice		$Mecp2^{tm1.1Bird}$ KO	6	F and M	[6–7 weeks]	Uncompensated sleep deprivation-like EEG biomarkers were found in the *Mecp2* KO mice

(Continues)

TABLE 1 (Continued)

Author	Country	Study field	Animal species	Modeling method	Mutation information	Number of mutated animals in sleep measurement	Gender of mutated animals	Age/weight of mutated animals (mean ± *SD*) [range]	Conclusions
Robinson et al. (2013)	Canada	Behavior	C57BL6/J/CBA mice	Female *Mecp2*^{Stop} mice silenced by insertion of a targeted *lox stop* cassette, crossed with males hemizygotes for the CreESR transgene	*Mecp2*^{Stop} (∓)	10	F	[6–9 months]	Circadian rhythms and amount of sleep was maintained in *Mecp2*^{Stop} mice, while overall locomotor activity reduced
Ren et al. (2012)	Canada	Respiratory dysfunction	Mice	*Mecp2* heterozygous female (*Mecp2*$^{tm1-1Jae}$) and WT male mice were obtained	*Mecp2*$^{tm1-1Jae}$ (-/y)		M	[32–115 days]	Sleep apneas started appearing and became more frequent and longer lasting with age in *Mecp2*$^{-/y}$ mice
Wither et al. (2012)	Canada Behavior		C57BL/6 mice		*Mecp2*$^{tm1.1Bird}$, *Mecp2*^{tm2Bird}	7 4	F	[300–400 days]	MeCP2 deficiency is sufficient to alter the normal daily cyclic patterns of cortical delta wave activity
D'Cruz et al. (2010)	Canada	Electroencephalogram EEG	C57BL/6 mice	Crossing female *Mecp2*$^{-/+}$ *mice (Mecp2*$^{m1.1Bird}$*) with male wild-type mice*	*Mecp2*$^{tm1.1Bird}$ (−/+)(−/y)		F and M	[F: 8–12 months] [M: 50–70 day]	During acute sleep, MeCP2-deficient mice displayed normal delta-like activity in cortex and sharp wave activity in hippocampus and somatosensory cortex
Moretti et al. (2005)	United States	Behavior	C57BL/6J mice	Crosses of heterozygous *Mecp*$^{2308/X}$ mutant females with wild-type males	*Mecp2*$^{308/Y}$ (truncating mutation)	12	M	10 weeks/21 + 0.8gr	Relative hypoactivity during dark and hyperactivity in light of *Mecp2*$^{308/Y}$

Abbreviations: *Cdkl5*, cyclin-dependent kinase like 5; EEG, electroencephalogram; F, female; KO, knock out; M, male; *Mecp2*, methyl-CpG-binding protein 2; NREM, non-rapid eye movement sleep; SCN, suprachiasmatic nucleus; WT, wild type.

Drosophila (Gupta, Morgan, Bailey, & Certel, 2016; Hess-Homeier, Fan, Gupta, Chiang, & Certel, 2014), and 10 using mice (D'Cruz et al., 2010; Fuchs et al., 2018; Johnston et al., 2014; Li et al., 2015; Lo Martire et al., 2017; Moretti, Bouwknecht, Teague, Paylor, & Zoghbi, 2005; Ren, Ding, Funk, & Greer, 2012; Robinson, Plano, Cobb, & Riedel, 2013; Tsuchiya et al., 2015; Wither et al., 2012).

3.2 | Characteristics of the studies included

All 13 studies were performed with wild type (WT) or control(s). The background of animal strains was clearly reported in all studies but one (Ren et al., 2012) which had no detailed information on its mice. Average range of age for seven mouse studies (D'Cruz et al., 2010; Johnston et al., 2014; Li et al., 2015; Ren et al., 2012; Robinson et al., 2013; Tsuchiya et al., 2015; Wither et al., 2012) was from 113.8 ± 109.8 to 180 ± 130.8 days, based on the age time quantum (ranging from 21–400 days). The study (Chen et al., 2017) with monkey model did not report such information. Weight reported in two mouse studies (Lo Martire et al., 2017; Moretti et al., 2005) was 23.3 ± 3.2 g. Across the 10 studies in mouse, no gender distribution difference was noticed, that is, three in female, four in male, and three in both. The sample size was only reported in one study being five female monkeys (Chen et al., 2017). While, sample size was available in eight mouse studies ranging from 4 to 31. For the two studies in *Drosophila*, using only males, the sample size ranged between 21 to 50 (Gupta et al., 2016) and 30 (Hess-Homeier et al., 2014).

3.3 | Establishment of animal models

Methods for generating the animal model was reported in 8/11 (Chen et al., 2017; D'Cruz et al., 2010; Fuchs et al., 2018; Li et al., 2015; Moretti et al., 2005; Ren et al., 2012; Robinson et al., 2013; Tsuchiya et al., 2015) studies except for the *Drosophila*. These models, were roughly gene edition, embryo implantation, female recessive homozygote to female heterozygote mutants or male mouse hemizygotes. Three studies (Johnston et al., 2014; Li et al., 2015; Lo Martire et al., 2017) reported in detail the number of 3, 7, 9 generations backcrossed to maintain a pure genetic background.

Regarding the mutations, only two studies focused on the *Cdkl5* gene (Fuchs et al., 2018; Lo Martire et al., 2017), while the majority (11/13) of animals were modeled on *Mecp2* mutations. In monkeys, TALENs edited missense, nonsense mutations, and/or indels on exon 3 of the *MECP2* gene were applied (Chen et al., 2017). In mice, for *Mecp2* gene lack/deficient (D'Cruz et al., 2010; Ren et al., 2012; Robinson et al., 2013; Tsuchiya et al., 2015; Wither et al., 2012) or truncated transcription (Johnston et al., 2014; Li et al., 2015; Moretti et al., 2005) mutations and for *Cdkl5* knockout (KO) models (Fuchs et al., 2018; Lo Martire et al., 2017) were used. CRISPR/Cas-mediated system was applied in two of these mouse studies, respectively (Robinson et al., 2013; Tsuchiya et al., 2015). In *Drosophila*, human methyl-CpG-binding protein 2 (hMeCP2) (Gupta et al., 2016; Hess-Homeier et al., 2014) was induced to express related domains.

The procedure of mutation confirmation was stated in seven studies (Chen et al., 2017; Fuchs et al., 2018; Hess-Homeier et al., 2014; Johnston et al., 2014; Moretti et al., 2005; Tsuchiya et al., 2015; Wither et al., 2012).

3.4 | Study methodology

None of the included studies was interventional but performed comparisons with WT in mice and monkeys or with control group(s) in *Drosophila*. Two studies (D'Cruz et al., 2010; Ren et al., 2012) did not report information of animal housing conditions (e.g., 12:12 light/dark cycle). All the studies made the ethics statements but one (Moretti et al., 2005), currently for *Drosophila* studies this is not required (Gupta et al., 2016; Hess-Homeier et al., 2014). The methods of sleep assessments and statistical calculations were described in all 13 studies with 6 (Chen et al., 2017; D'Cruz et al., 2010; Fuchs et al., 2018; Johnston et al., 2014; Li et al., 2015; Moretti et al., 2005) blinded to outcome assessments.

3.5 | Findings in *Drosophila*

Hess-Homeier et al. (2014) and Gupta et al. (2016) conducted studies in *Drosophila* with hMeCP2 expression. Sleep bout was determined as complete inactivity for a period of 5 consecutive minutes recorded by the *Drosophila* Activity Monitoring (DAM) system.

3.5.1 | Sleep duration expressed as sleep bouts

Hess-Homeier et al. (2014), found that total time spend in sleep during a 24-hr period was significantly reduced but could not confirm fragmented sleep bouts. Whereas in Gupta et al. (2016), sleep was significantly deficient and fragmented by increased average number of sleep bouts and decreased bout length across the day–night time frame.

3.5.2 | Sleep onset

Reduced latency to initiate sleep was reported in one study (Gupta et al., 2016).

3.5.3 | Other sleep-related findings

No sleep changes were found when hMeCP2 was expressed in serotonin neurons compared to octopamine neurons. Gradual manipulation of the sensitive domains, that is, being full-length hMeCP2 as

TABLE 2 Summary of findings in mouse model

Parameter	Index	Mutation type	Assessment	Findings compare to WT
Activity amount, (duration, distance. count) (Li et al., 2015; Moretti et al., 2005; Robinson et al., 2013; Tsuchiya et al., 2015; Wither et al., 2012)	Amount of activity (rev/hr) (LD↓/DD↓) Distance moved (cm) (L/D↓) Time in patrolling zone (s) (Locomotion) ↓ Progressive movements (ambulation) (L/D↓) Fine movements (lingering) (L/D↓)	*Mecp2*$^{tm1.1Jae}$/Mmucd (Li et al., 2015) *Mecp2*$^{Stop/+}$ (Robinson et al., 2013)	Video, wheel running assay (Li et al., 2015) PhenoMaster/LabMaster, PhenoTyper (Robinson et al., 2013)	The amount of activity (rev/hr) is significantly reduced in the mutants in both LD and DD conditions (Li et al., 2015) Reduction in both ambulation and fine movement during darkness (Robinson et al., 2013)
	Total activity (/hr) (L↑/D↓) Locomotor activity (/hr) (L↓/D) Fine movements (/hr) (L↑/D)	*Mecp2*$^{308/Y}$ (Moretti et al., 2005)	Photobeam Activity System (Moretti et al., 2005)	Same activity over 24 hr; relative hypoactivity in dark phase and hyperactivity in the light phase of *Mecp2*$^{308/Y}$ (Moretti et al., 2005)
	Average activity state duration (hr) (Total↓/L/D↓) 30s-segments with mobility per day (Total↓/L↓/D↓) Mobility sum (arb. units) (Total↓/L↓/D↓)	*Mecp2*$^{tm1.1Bird}$, *Mecp2*^{tm2Bird} (Wither et al., 2012)	EEG (Wither et al., 2012)	No difference in total mobility cycles over the 24-hr; significantly decreased average duration of the active state of a cycle; *Mecp2*$^{\mp}$ mice exhibited similar active state durations in both light and dark phases (Wither et al., 2012)
	Activity counts (DD) (CT0–24↓/0–12↓/12–24↓) Period length (DD) (hr)	*Mecp2*-deficient (Tsuchiya et al., 2015)	Infrared motion (Tsuchiya et al., 2015)	Less active throughout whole circadian day, same period length, and less active throughout a day under DD conditions (Tsuchiya et al., 2015)
Activity frequency (number) (Li et al., 2015; Robinson et al., 2013)	Fragmentation (bouts/day) (LD↑/DD↑)	*Mecp2*$^{tm1.1Jae}$/Mmucd (Li et al., 2015)	Video, wheel running assay (Li et al., 2015)	*Mecp2*$^{-/y}$ mutants' activity rhythms were significantly more fragmented under bother LD and DD conditions (Li et al., 2015)
	Frequency in patrolling	*Mecp2*$^{Stop/+}$ (Robinson et al., 2013)	PhenoMaster/LabMaster, PhenoTyper (Robinson et al., 2013)	*Mecp2*^{stop} mice enter the patrolling zone with the same frequency with WT (Robinson et al., 2013)
Activity power (Li et al., 2015; Tsuchiya et al., 2015; Wither et al., 2012)	Activity power (rhythm amplitude, %V) (LD↓/DD↓)	*Mecp2*$^{tm1.1Jae}$/Mmucd (Li et al., 2015)	Video, wheel running assay (Li et al., 2015)	Significantly reduced strength (power) of locomotor activity under both LD and DD conditions (Li et al., 2015)
	Rate of mobility (magnitude of movement per second (arb. units/s) (Total↓/L/D↓)	*Mecp2*$^{tm1.1Bird}$, *Mecp2*^{tm2Bird} (Wither et al., 2012)	EEG (Wither et al., 2012)	The average rate of movement by the *Mecp2*$^{\mp}$ mice was diminished most pronounced in the dark phase (Wither et al., 2012)
	Periodogram amplitude (Qp value) (DD↓)	*Mecp2*-deficient (Tsuchiya et al., 2015)	Infrared motion (Tsuchiya et al., 2015)	Significant changes (lower) in the periodogram amplitude (Qp value) in DD condition (Tsuchiya et al., 2015)

(Continues)

TABLE 2 (Continued)

Parameter	Index	Mutation type	Assessment	Findings compare to WT
Activity related (Li et al., 2015; Robinson et al., 2013)	Precision (min) (LD↓/DD↓)	*Mecp2*$^{tm1.1Jae}$/Mmucd (Li et al., 2015)	Video, wheel running assay (Li et al., 2015)	*Mecp2*$^{-/y}$ mutants' activity rhythms were lower precision under both LD and DD conditions (Li et al., 2015)
	Time in food zone (%)↑ Cumulative food intake (g) (L/D↑)	*Mecp2*$^{Stop/+}$ (Robinson et al., 2013)	PhenoMaster/LabMaster, PhenoTyper (Robinson et al., 2013)	Increased food intake due to nocturnal eating during darkness in *Mecp2*^{Stop} (Robinson et al., 2013)
EEG wave frequency (Johnston et al., 2014; Wither et al., 2012)	Delta power ratio sleep/wake (Total↓/1 Hz/2 Hz/4 Hz↓)	*Mecp2*$^{tm1.1Bird}$ KO (M. Johnston et al., 2014)	EEG (Johnston et al., 2014; Wither et al., 2012)	Lower power in the 4 Hz frequency SWA range (Johnston et al., 2014)
	Delta power (mV2/Hz) (L/D)	*Mecp2*$^{tm1.1Bird}$, *Mecp2*^{tm2Bird} (Wither et al., 2012)		Significant decrease in the average number of delta cycles over a 24 hr period (Wither et al., 2012)
EEG parameter duration (D'Cruz et al., 2010; Wither et al., 2012)	Inter- sharp wave interval (s)	*Mecp2*$^{tm1.1Bird}$ (–/+) (–/y) (D'Cruz et al., 2010)	EEG (D'Cruz et al., 2010; Wither et al., 2012)	
	Average State non-delta Duration (hr) (Total↑/L↑/D↑)	*Mecp2*$^{tm1.1Bird}$, *Mecp2*^{tm2Bird} (Wither et al., 2012)		Longer of average duration of the non - delta state of each cycle period over a 24 hr period (Wither et al., 2012)
Sleep apneas frequency (Fuchs et al., 2018; Lo Martire et al., 2017; Ren et al., 2012)	Frequency (cycle/min) (24 days after respiratory dysfunction) ↑ Number of Apneas/hr (total sleep. NREM, REM) ↑ Breathing frequency (12 days after respiratory dysfunction) ↑	*Mecp2*$^{tm1-1Jae}$ (–/y) (Ren et al., 2012)	EEG, EMG (Ren et al., 2012)	Sleep apneas started and became more frequent with age in *Mecp2* (Ren et al., 2012)
	Number of apneas/h (TOTAL↑/ NREM↑/REM↑) Occurrence rate of other apnea/hr (NREM) ↑	*Cdkl5* KO (Lo Martire et al., 2017)	WBP (Fuchs et al., 2018; Lo Martire et al., 2017)	More frequent apneas during NREM sleep than total sleep, REM sleep *Cdkl5* KO mice (Lo Martire et al., 2017)
	Number of apneas/h (Total sleep↑/NREM↑/REM)	*Cdkl5*$^{-/+}$, *Cdkl5*$^{-/-}$ (Fuchs et al., 2018)		More frequent apneas during NREM and total sleep in *Cdkl5* KO mice (Fuchs et al., 2018)
Sleep apneas duration (Lo Martire et al., 2017; Ren et al., 2012)	Instantaneous total breath duration (T_{TOT}) ↓ Duration of other apneas (ms) (REM) ↓	*Cdkl5* KO (Lo Martire et al., 2017)	WBP (Lo Martire et al., 2017)	Higher occurrence rate of the apneas that did not follow a sigh during NREM sleep; shorter duration of the apneas that did not follow a sigh during REM sleep (Lo Martire et al., 2017)
	Apneas duration (min) (12 days after respiratory dysfunction) ↑ Relative minutes ventilation (12 days after respiratory dysfunction) ↓	*Mecp2*$^{tm1-1Jae}$ (–/y) (Ren et al., 2012)	EEG, EMG (Ren et al., 2012)	Aggravation of sleep apneas with age (Ren et al., 2012)

Note: ↑: mutant animals showed significant higher than WT; ↓: mutant animals showed significant lower than WT.

Abbreviations: AUC, area under the curve; *Cdkl5*, cyclin dependent kinase like 5; DD, constant dark; EEG, electroencephalogram; EMG, electromyogram; h, hour; KO, knock out; L, light, D, dark; LD, 12:12 light/dark; *Mecp2*, methyl-CpG binding protein 2; min, minutes; NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep; rev: revolutions per 3 min intervals; s, second; SCN, suprachiasmatic nucleus; SWA, slow wave activity; T_{TOT}, instantaneous total breath duration; VE, minute volume per unit body weight; VT, tidal volume per unit body weight; WBP, Whole-body plethysmography; WT, wild type.

well as *dMBD-R2* and *dMBD2/3* domains (Gupta et al., 2016) revealed *dMBD-R2* and *hMeCP2*-mediated phase-specific sleep deficits: abnormalities in sleep bouts and sleep duration. Hence, these domains likely target common neuronal functions, whereas overexpression of *dMBD2/3* showed reduction and fragmentation of sleep.

3.6 | Findings in cynomolgus monkey

Chen et al. (2017) applied behavioral analyses for sleep in their *MECP2* mutant monkey models. Sleep patterns were determined as follows: awake and sleep phases including relaxed and transitional sleep.

3.6.1 | Sleep duration

Although the authors scored longer awake (and shorter sleep) duration at night, there were no significant differences when compared with WT counterparts.

3.6.2 | Sleep bouts

Substantially more frequent sleep bouts (no specific definition for bouts) per night as well as more frequent naps were noticed.

Overall, the authors described a fragmented sleep status or disabled maintenance of long-hour sleep. No detailed information of sleep stages is available for this study.

3.7 | Findings in mouse

Eight of 10 studies in mice involved *Mecp2* mutation (D'Cruz et al., 2010; Johnston et al., 2014; Li et al., 2015; Moretti et al., 2005; Ren et al., 2012; Robinson et al., 2013; Tsuchiya et al., 2015; Wither et al., 2012) whereas the two others dealt with that of *Cdkl5* (Fuchs et al., 2018; Lo Martire et al., 2017). The topic of mouse studies could be subdivided into three fields: circadian, EEG, and respiratory. Because the majority of studies included in this review are on mouse models, their findings have been summarized in Table 2.

Data directly describing changes in sleep patterns were scant, and studies primarily investigated circadian rhythm. Five of these studies (Li et al., 2015; Moretti et al., 2005; Robinson et al., 2013; Tsuchiya et al., 2015; Wither et al., 2012) investigated activity regulation over 24 hr in *Mecp2* mutant mice using different indices of circadian rhythm. Despite applying a different index, they each concluded disturbed or impaired circadian rhythm.

3.7.1 | Sleep duration

Only three studies investigated sleep duration (Johnston et al., 2014; Li et al., 2015; Lo Martire et al., 2017). Mouse models revealed unaltered percentage/duration of sleep within 24 hr. Yet in one of them, a significantly enhanced waking state (i.e., WT shows some sleeping) and a shorter duration of REM sleep cycles compared to the WT were reported (Johnston et al., 2014). Regarding the average sleep bout duration, one study reported shorter duration with increased sleep bout number across the 24 hr (Li et al., 2015).

3.7.2 | Sleep onset

Two studies reported a prolonged sleep onset latency (M. V. Johnston et al., 2014; Li et al., 2015).

3.7.3 | Circadian rhythm

Four of the five studies analyzed circadian rhythm via behavioral analysis and one study applied EEG (Wither et al., 2012). Impaired circadian rhythm was expressed as decreased locomotor activity amount (Li et al., 2015; Robinson et al., 2013; Tsuchiya et al., 2015; Wither et al., 2012) and rhythm amplitude (Li et al., 2015; Tsuchiya et al., 2015; Wither et al., 2012). That is, significantly more fragmented and lower precision of circadian activity rhythm was identified, irrespective of light–dark conditions. The specific genotype of *Mecp2*$^{308/Y}$ compared to WT showed hypoactivity in the dark phase and hyperactivity in the light phase (Moretti et al., 2005). Overall, findings indicate that the mutant mice had poor intrinsic circadian rhythm to maintain an appropriate and stable locomotor activity amount and rhythmicity.

3.7.4 | EEG analysis

Three studies (D'Cruz et al., 2010; Johnston et al., 2014; Wither et al., 2012) applied power spectral analysis. Two of them noticed three features regarding the delta waves: (a) lower power in the 4 Hz frequency SWA (Johnston et al., 2014), (b) significant decrease in the average number of delta cycles over a 24-hr period (Wither et al., 2012), (c) longer average duration of the non-delta state of each cycle period (Wither et al., 2012). Another one detected that *Mecp2* mutant mice displayed normal delta and sharp wave activity in the hippocampus and somatosensory cortex during sleep period (D'Cruz et al., 2010).

3.7.5 | Breathing during sleep

Three studies, of which two were on *Cdkl5* gene silencing (Fuchs et al., 2018; Lo Martire et al., 2017), and one on *Mecp2* gene mutation (Ren et al., 2012) reported respiratory dysfunction and abnormal breathing patterns during sleep. Those with *Cdkl5* mutation confirmed sleep apneas appearing more often in NREM than REM

sleep. In the *Mecp2* mutant mice progressive respiratory dysfunction was detected, that is, sleep apneas became more frequent and longer lasting with age, about 1–3 weeks after apneas during wakefulness appeared.

Based on the fly models, sleep bouts appear to be regulated by *MECP2*, suggestive of its role in sleep continuity. Overall, given the monkey and mouse models, total sleep duration across 24 hr appears unaltered. However, both the sleep and wake state are impaired, with predominantly a fragmented sleep state. In addition, a weakened circadian activity rhythm is seen.

Few studies have investigated sleep structure. Regards NREM, delta power showed a marked decrease and sleep apneas were more probable. Other scant results are speculative of a more pronounced wake state and shorter REM cycles.

4 | DISCUSSION

The discovery of the genetic pathophysiology of RTT offers possibilities to design animal models, and in keeping with the disease pathogenesis, the majority of studies were performed in *Mecp2* mutant animals. These models successfully mimicked per gender (Young & Zoghbi, 2004) and genotypes (Gupta et al., 2016; Watson et al., 2005) several manifestations of RTT; that is, being apparently normal early development and progressive regression of locomotor function and particularly irregular breathing (Chen et al., 2001; Guy et al., 2001). Noteworthy the mouse model is most commonly used in current animal studies. More recently, newer gene targeting tools (e.g., TALENs and CRISPR/Cas-mediated system) generating mutant animals have been successfully implemented in RTT animal sleep research (Chen et al., 2017; Tsuchiya et al., 2015).

Reviewing the RTT animal model studies on sleep, we confirm problematic sleeping, which can be generally characterized as disturbed sleep efficacy and continuity. More specifically, we may conclude comparable total sleep duration and a preserved sleep/wake proportion over the 24 hr, yet with increased number of sleep bouts (or hence wake times). Such highly fragmented sleep, challenges the sleep compensation ideas in RTT animal models. Similarly perturbed is the circadian rhythm, a likely mechanism affecting both the sleep–wake cycle and activity rhythmicity. Another important finding issued from EEG power spectral analysis, was the decreased number and power of delta waves. The *Cdkl5* KO mouse models were primarily used to identify the respiratory dysfunction during sleep (Fuchs et al., 2018; Lo Martire et al., 2017), showing more frequent and longer duration of apneas in NREM sleep aggravating with age.

4.1 | Characteristics of sleep in animal models of RTT

Night time sleep abnormalities including increased number of wake bouts, emerged across the three categories of animal models reported in this review (Chen et al., 2017; Gupta et al., 2016; Hess-Homeier et al., 2014; Johnston et al., 2014; Li et al., 2015). Both mutant monkey and mouse models (Chen et al., 2017; Li et al., 2015) suggested the trend of decreasing sleep bout duration and increasing bouts number. Such increased number of sleep bouts, that is, sleep fragmentation ascribed to more frequent nocturnal awakenings, concurs with complaints of night waking reported in individuals with RTT (Carotenuto et al., 2013; Glaze, Frost, Zoghbi, & Percy, 1987; Hagebeuk et al., 2013; Sarber, Howard, Dye, Pascoe, & Simakajornboon, 2019). Furthermore, human MeCP2 overexpression in *Drosophila* showed an impact on sleep continuity, while the prolonged sleep onset latencies and attenuated delta power in mice in particular suggest poor sleep state efficacy. Such sleep abnormalities put forward adverse effects of *Mecp2* on sleep propensity regulation. This may also support some inconsistencies regarding wake duration: that is, longer waking period with (Johnston et al., 2014) or without (Chen et al., 2017) significant differences when compared to WT/control(s). Possibly glutamate dysfunction in the frontal cortex of *Mecp2*-null mice, which likely becomes toxic for the function of synapses over a period of time (Dash, Douglas, Vyazovskiy, Cirelli, & Tononi, 2009), may underlie the long wake state and poor quality of SWS.

The sleep problems summarized here suggest that the mutated RTT animal models cannot maintain a consolidated sleep as demonstrated by disturbed night time sleep duration and mis-distributed awaking during the nocturnal phase, in spite of comparable sleep/wake time durations as reported in WT/control(s). Furthermore, mutated animals exhibited unenhanced sleep rebound as shown by possible longer sleep latency but foremost longer duration of wake cycles indicating impaired sleep homeostasis.

4.2 | EEG alterations in animal models of RTT

Local high-frequency oscillations, or sharp waves, might be markers of seizure onset zones in an epileptic brain. However, they can be recorded also in nonepileptic cerebral structures. Alternatively, vertex sharp transient discharges are considered an early marker of NREM sleep. Consequently, the sharp waves reported during acute sleep in MeCP2-deficient mice need further investigation. For instance, EEG affected by epileptic seizures is quite prevalent in RTT, such spikes and sharp waves, likely epileptiform transients, may resemble the interictal marker of an individual with RTT suffering epilepsy.

Findings indicating delta wave attenuation and longer non-delta state across sleep cycles may underpin the severe deprivation of SWA along with the poor quality of SWS (or deep sleep). Moreover, in integrating our previous section about their poor sleep continuity/consolidation and in accordance to sleep deprivation research (Franken, Chollet, & Tafti, 2001; Franken, Dijk, Tobler, & Borbely, 1991), increased sleep intensity after sleep deprivation should be demonstrated. That is, a proportional increase in delta power is evoked by sleep loss while excess sleep creates a decrease

in delta power (Franken et al., 2001). SWA further intensifies as a function of prior wake state. Therefore, delta power is thought to reflect deep sleep need and its underlying sleep regulating recovery processes (Franken et al., 1991). RTT mutant mice should consequently present increased proportion of delta power and deep sleep. Contrariwise studies also reported longer wake status instead. This potentially illustrates the absence of sleep compensatory mechanisms or impaired sleep homeostasis in RTT animal (more specifically, mice) models.

Some studies in individuals with RTT have reported abnormal EEG/PSG to demonstrate the disturbed sleep structure (Amaddeo et al., 2019; Grosso et al., 2007; Hagebeuk et al., 2013; Marcus et al., 1994) or/and poor sleep alike decreased sleep spindles or REM sleep (Espinar-Sierra et al., 1990; Garofalo, Drury, & Goldstein, 1988), and increased sharp waves during NREM sleep (Aldrich, Garofalo, & Drury, 1990; Ammanuel et al., 2015; Cooper, Kerr, & Amos, 1998). Contrariwise to the animal studies, several studies reported heightened delta power (Ammanuel et al., 2015; Cooper et al., 1998; Trauner & Haas, 1987) with fewer SWS cycles (Ammanuel et al., 2015).

The neural mechanisms underlying the sleep–wake problems of RTT animal models remain to be fully investigated. Wakefulness and cortical activation are maintained by the ascending activating influx arising from the basal forebrain, thalamus, posterior hypothalamus, and brainstem with the involvement of quite many neurotransmitters and neuropeptides (Brown, Basheer, McKenna, Strecker, & McCarley, 2012; Lin, Anaclet, Sergeeva, & Haas, 2011; Saper, Fuller, Pedersen, Lu, & Scammell, 2010). The cessation of activities of the above-mentioned ascending activating systems constitutes a prerequisite for sleep onset (Saper et al., 2010; Steriade, 1992). Several brain areas are known for their major role in sleep generation such as the preoptic and anterior hypothalamus containing inhibitory gamma-aminobutyric acid (GABA) and galanin neurons; that is, medullary GABAergic parafacial zone particularly for SWS and the mesopontine tegmentum particularly for REM sleep (Brown et al., 2012; Lu, Sherman, Devor, & Saper, 2006; Saper et al., 2010). The neurophysiological mechanisms involved in the generation of cortical slow waves and spindles (both part of NREM sleep) are distinct, but both of them likely depend on the hyperpolarization of the thalamocortical axis (Buzsaki et al., 1988; Dijk, Hayes, & Czeisler, 1993; Williams, Turner, & Crunelli, 1995). Overall, sleep "on" areas are firstly disinhibited by the ascending activating systems allowing sleep onset and then they would in turn actively inhibit those arousal systems allowing sleep to be maintained (Saper, Chou, & Scammell, 2001).

Mecp2 plays a role in neuronal proliferation, migration, and differentiation since embryotic period (Cobolli Gigli et al., 2018; Ehinger, Matagne, Villard, & Roux, 2018; Kishi & Macklis, 2004). For instance, MeCP2 is also critical for normal functioning of GABA-releasing neurons (Chao et al., 2010). The failure of *Mecp2* and other genes in the above-mentioned brain areas critically involved in sleep–wake control would allow explaining the sleep–wake problems associated with RTT. Of note, the marked sleep fragmentation demonstrated in several studies with RTT animal models is reminiscent of that seen with KO mice with impaired brain ascending activating systems such as those lacking the neuropeptides orexins and their receptors, the neurotransmitter histamine and its receptors and 5-hydroxy tryptamine (5HT) receptors (Lin et al., 2011; Saper et al., 2001, 2010), or sleep-promoting inhibitory neurons (Lu, Greco, Shiromani, & Saper, 2000).

4.3 | Circadian rhythmicity

The manifestation of sleep tightly relates to circadian rhythm (Hastings, Reddy, & Maywood, 2003). Because circadian rhythm is highly regulated by light (Azzi et al., 2014), a well-regulated housing condition is an important prerequisite to investigate the circadian rhythm of animals. 84.6% of selected articles clearly stated they are housing animals in a 12:12 LD cycle environment since birth. Hence, such animal experiments control the potential influence from environment to maintain the natural circadian rhythm on sleep.

In this realm, the mutant mice in particular showed abnormalities in rhythms of locomotor activities per behavioral and EEG analysis in both LD and DD conditions, that is, weakened activity rhythm. These findings suggest that the robustness of the SCN, pacemaker of circadian rhythm, is possible damaged in *Mecp2*-deficient animal models (Tsuchiya et al., 2015). *Mecp2* is reported to be substantially expressed in the SCN (Dragich, Kim, Arnold, & Schanen, 2007). But SCN modulates for instance also melatonin secretion, that induces the timing of endogenous circadian phase and period. Alternatively, exogenous melatonin is commonly given to children with developmental disabilities to facilitate falling asleep (Angriman, Caravale, Novelli, Ferri, & Bruni, 2015). Impaired SCN were demonstrated in mouse brain frontal cortices (Martinez de Paz et al., 2015). Consequently, the deficits in SCN amount or activity will therefore provoke deficits of circadian rhythmicity and even sleep pressure because of such direct or indirect SCN perturbations. No information regarding *Cdkl5* mutations and circadian rhythmicity could be retrieved from the literature; *CDKL5* is known as a phosphorylation mediator in the molecular pathway of *MECP2* (Mari et al., 2005).

Characteristic to individuals with RTT are the severe physical disabilities (Killian et al., 2017; Kyle, Vashi, & Justice, 2018), which are potentially represented in the animal models (Bhattacherjee et al., 2017). Therefore, the poor activity rhythm could be due to SCN dysfunction and motor system impairments combined, or even other currently unknown factors. Behavioral analyses of locomotion, as an indicator of circadian rhythmicity, have often been applied to objectify the amount of "sleep" in most (4/5) of the studies reviewed. Hence, while applying this behavioral analysis, a potentially affected motor system needs to be acknowledged. Future studies applying around the clock registration by EEG in particular could for that reason assist in generating more specific sleep–wake cycle data.

4.4 | Breathing abnormalities during sleep

All of the three studies examining respiratory function (Fuchs et al., 2018; Lo Martire et al., 2017; Ren et al., 2012) confirmed the occurrence of sleep apneas, a finding that is also reported in several human studies (Amaddeo et al., 2019; Glaze et al., 1987; Hagebeuk et al., 2012, 2013). In mutant animal models, apneas tend to be more frequent in NREM sleep compared to their total sleep period distribution or REM sleep distribution (Fuchs et al., 2018; Lo Martire et al., 2017), which contradicts most of human (non-RTT) research about apnea distribution (Morielli, Ladan, Ducharme, & Brouillette, 1996; Spruyt & Gozal, 2012). In individuals with RTT, Marcus et al. (1994) concluded normal breathing during NREM sleep and speculated normal brain-stem control of ventilation. They, however, found slightly lower oxygen saturation during REM breathing patterns compared to female subjects with snoring but without obstructive apnea or gas exchange abnormalities. It was concluded as abnormal-developmental cortical influence on ventilation. Yet inconsistencies exist in the human literature. For instance, Glaze et al. (1987) only identified in 1 of 11 RTT individuals obstructive sleep apnea during REM.

Sleep apnea severity was further suggested to be positively correlated with age (Ren et al., 2012). The animal research also speculated that when RTT progressed to the late-stage deteriorative brainstem function it may worsen sleep apneas; for example, as the gradual *Mecp2* deletion disturbs the autonomic control of the brainstem (Ren et al., 2012). Yet other proposed factors may take part in the respiratory neuro-regulation systems including GABA, brain-derived neurotrophic factor (BDNF) and monoaminergic (Katz, Dutschmann, Ramirez, & Hilaire, 2009) modulators. Noteworthy for older individuals with RTT, the percentage of total sleep time was significantly reduced compared to younger individuals (Glaze et al., 1987), potentially affecting sleep respiratory findings. More studies are needed to investigate the discordance between animal and human findings.

4.5 | Limitations and future directions

Nearly all animal models are adult, while RTT expresses during childhood, a period where also the sleep structure undergoes drastic changes. We furthermore could retrieve limited information about REM sleep in the literature, despite being reported as seriously disturbed in human research. One of the reasons would be that current animal models are reflecting only in part RTT, for example, in animal models one may alter a single gene whereas in RTT likely more genes are affected (Ehrhart et al., 2016). Alternatively, the brain structures responsible for REM sleep generation and maintenance such as the mesopontine tegmentum (Yamada & Ueda, 2019) may show minimal misexpression by the gene(s). No publications on *Foxg1* mutation models investigating sleep were found.

The methodological quality applied in animal experiments and reports was difficult to assess primarily due to incompleteness. Although animal studies differ from human research, several standard practices could be followed (Hooijmans et al., 2014); for example, blinding (Kilkenny et al., 2009). Due to differences in research quality, several biases (e.g., the operationalization of sleep parameters) could confound the results. Subsequently, the reliability and efficiency of translating animal research into clinical practice may be hampered. We therefore advocate for more consistency in reporting (e.g., the different timing of animal age) experiments, as well as in defining outcomes (e.g., sleep parameters investigated). A better streamlining of experiments may generate more consistent results, potentially across species. Lastly, studies provided scant discussion on the neural mechanistic pathways, hence future studies may elaborate on this aspect.

4.6 | Conclusion

A profile of fragmented and poor-quality sleep of RTT animal models could be summarized. First, RTT animal models exhibited disturbed sleep behavior as characterized by more frequent nocturnal awakenings within the 24-hr cycle time; second, RTT animal models showed poor ability to maintain sufficient sleep based on the high number of bouts and possibly also their shortened duration; these two points are consistent with a marked sleep fragmentation or poor sleep maintenance. Third, RTT animal models exhibited compromised sleep quality and absent sleep rebound based on the significant decreased delta power, as well as longer sleep onset latency (in *Mecp2* mutant mouse model), which is consistent with an impaired sleep homeostasis. Fourth, RTT animal models showed impaired circadian rhythmicity as attenuated locomotor activity with fragmentated and less precise rhythm. Lastly, RTT animal models exhibited sleep breathing abnormalities particularly during NREM.

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CONFLICT OF INTEREST

The author(s) declare(s) that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

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