Sleep disorders in Rett's syndrome

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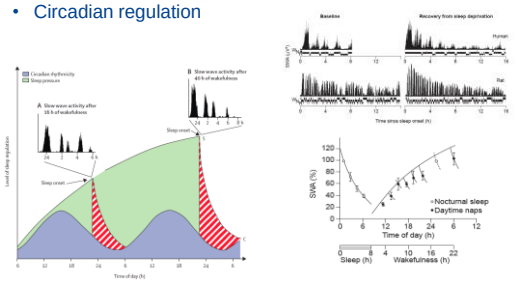
Goals of Presentation

- To identify mechanism involved in the two process model: homeostatic regulation (wake-sleep) and circadian regulation
- To identify common sleep disorders associated with Rett's syndrome and their association to abnormalities in these regulations.

The Two-process model and effect of sleep deprivation on SWS

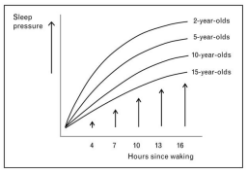
- Homeostatic regulation
- Circadian regulation



Borbely AA (1982) A two process model of sleep regulation. Hum Neurobiol 1:195-204. Dijk DJ. J Clin Sleep Med. 2009 Apr 15;5(2 Suppl):S6-15

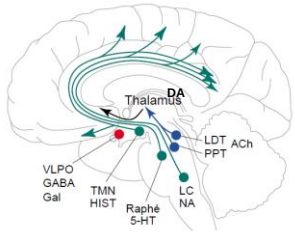
Homeostatic regulation

Sleep homeostasis and age



Jenni et al. Curr Opin Psychiatry. 2006 May; 19(3): 282–287.

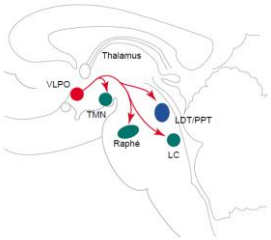
Neurobiology of wakefulness - Ascending Reticular Activating System



VLPO = Ventrolateral preoptic nucleus; TMN = Tuberomammillary nucleus; LDT = laterodorsal tegmental nucleus; PPT = pedunculopontine tegmental nucleus; LC = locus coeruleus; Ach = acetylcholine; NA = noradrenaline; 5-HT = serotonin; HIST = histamine; Gal = galanine

Saper CB, et al. *Trends Neurosci* 2001;24:726-31

Neurobiology of sleepiness

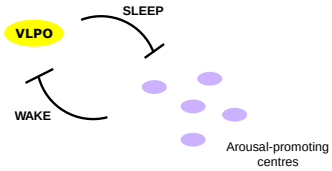


VLPO = Ventrolateral preoptic nucleus; TMN = Tuberomammillary nucleus;
LDT = laterodorsal tegmental nucleus; PPT = pedunculopontine tegmental nucleus; LC = locus coeruleus

Saper CB, et al. *Trends Neurosci* 2001;24:726-31

The sleep/wake flip-flop switch

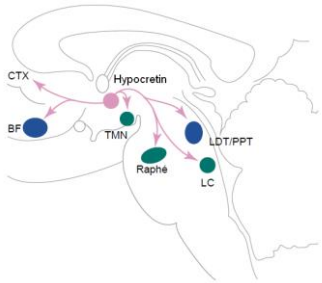
Pathways promoting wakefulness and sleepiness actively inhibit each other



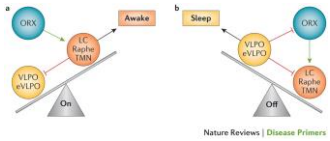
VLPO = Ventrolateral preoptic nucleus

Saper CB. *Prog Brain Res* 2006;153:243-52

The hypocretinergic (orexin) system

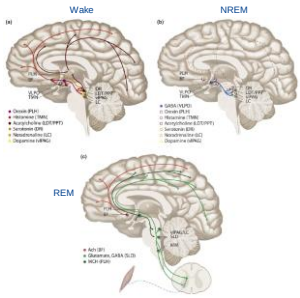


The flip-flop switch model



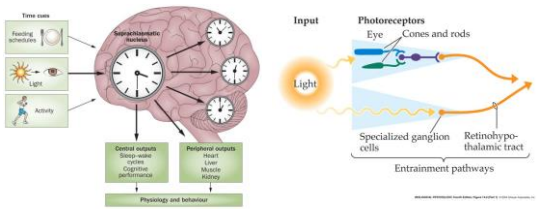
Saper, C. B., Scammell, T. E. & Lu, J. *Nature* 437, 1257–1263 (2005). Morin, C. M. *et al.* (2015) *Nat. Rev. Dis. Primers*

Neuroanatomy and neurochemistry of sleep-wake function



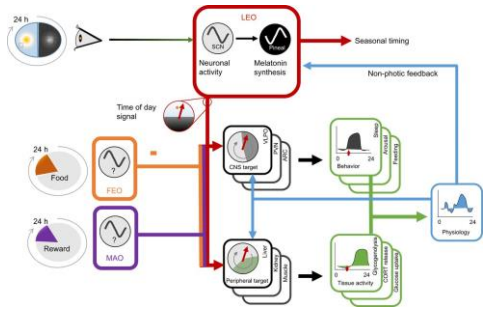
Bassetti CL,et al. Eur J Neurol. 2015 Oct;22(10):1337-54.

Circadian regulation



Videnovic et al. Nat Rev Neurol. 2014 Dec; 10(12): 683–693

Overview of the proposed hierarchical control of circadian rhythms in mammals.



Sjaak J. Riede et al. J Exp Biol 2017;220:738-749

Function of sleep

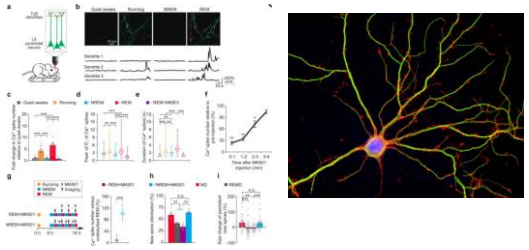
Sleep plays an active role in processes such as

- synaptic plasticity and memory functions,
- emotional regulation,
- metabolic functions and energy balance,
- macromolecule biosynthesis,
- removal of toxic substances and metabolic waste, or
- prophylactic cellular maintenance.

Default state of the organism/cerebral networks or a state of adaptive inactivity.

Vyazovskiy VV. Nat Sle Sci 2015 ; 7:171—184

REM sleep selectively prunes and maintains new synapses in development and learning



REM sleep has multifaceted functions in brain development, learning and memory consolidation by selectively eliminating and maintaining newly formed synapses via dendritic calcium spike-dependent mechanisms

Li et al. Nat Neurosci. 2017 Mar; 20(3): 427–437.

Common sleep problems in Rett syndrome

- Sleep problems/disturbances (insomnia, nighttime awakenings)
- Nocturnal screaming and laugphing
- Abnormal sleep behavior (bruxism, head banging)
- Seizures/epilepsy
- Sleep disordered breathing

- Electrophysiologic abnormalities

Determinants of sleep disturbances in Rett syndrome in relation to genotype

Occurrence and Frequency of Specific Sleep Problems Observed in 364 Individuals With Rett Syndrome

	Never n (%)	Has stopped n (%)	Sometimes [a] n (%)	Often [b] n (%)	Total [c] n
Night waking	69 (19.3)	79 (5.5)	97 (27.1)	173 (48.3)	358
Night laughing	70 (21.6)	74 (22.8)	140 (43.2)	64 (17.7)	362
Difficulty falling asleep	90 (24.8)	46 (12.6)	107 (29.5)	120 (32.5)	258
Teeth grinding	113 (31.4)	77 (21.4)	68 (19.2)	101 (28.1)	360
Seizure at night	167 (47.2)	62 (17.5)	87 (24.6)	38 (10.7)	354
Night screaming	189 (52.5)	78 (21.7)	62 (17.2)	31 (8.6)	360
Daytime napping	206 (57.2)	23 (6.1)	79 (21.9)	46 (12.8)	360
Difficulty waking	231 (65.1)	13 (3.7)	69 (19.4)	42 (11.8)	355

[a] Categorization of three responses into one group: "Less than once a month," "Monthly," and "Twice a month."
[b] Categorization of three responses into one group: "Once or more a week," "Nightly," and "More than once a night."
[c] Denominator varies for each sleep problem due to some missing data.

Comparing the Sleep Disturbance Total and Subscale Scores Between Our Cohort and the Normative Sample

	Our cohort [a] (n = 326) Mean (SD)	Normative sample [b] (n = 1,157) Mean (SD)	*P* value
Total sleep score	10.07 (3.69)	7.98 (1.28)	<0.001
DIMS score	1.92 (0.77)	1.41 (0.44)	<0.001
SBD score	1.73 (0.86)	1.26 (0.40)	<0.001
DA score	1.21 (0.58)	1.10 (0.28)	<0.001
SWTD score	1.95 (0.75)	1.39 (0.40)	<0.001
DOES score	1.87 (0.75)	1.42 (0.51)	<0.001
SHY score	1.32 (0.64)	1.44 (0.85)	0.017

SD, standard deviation; DIMS, disorders of initiating and maintaining sleep; SBD, sleep breathing disorders; DA, disorders of arousal; SWTD, sleep-wake transition disorders; DOES, disorders of excessive somnolence; SHY, sleep hyperhydrosis
[a] Sample with Rett syndrome.
[b] Sample from general population (Bruni et al., 1996).

The prevalence of most sleep problems was highest in those with a p.Arg294 mutation.*
Severe epilepsy was associated with poorer sleep and impaired mobility with increased somnolence.

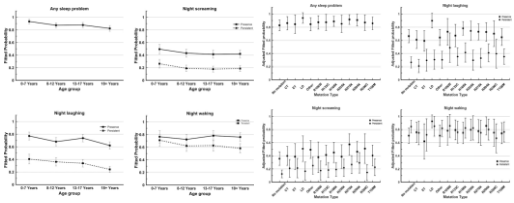
Boban et al. Am J Med Genet A. 2016 Sep;170(9):2292-300

The trajectories of sleep disturbances in Rett syndrome

(12 years from 320 families registered with the Australian Rett Syndrome Database)

Fitted probabilities of any sleep problem, night laughing, night screaming and night waking*, by age group and deletion

Aged adjusted fitted probabilities of any sleep problem, night laughing, night screaming and night waking*, by mutation type



Wong et al. J Sleep Res. 2015 Apr;24(2):223-33

Electrophysiological findings in RTT

- Focal and generalized slow activity
- Focal, continous spike activity
- Continued spike and wave in slow-wave sleep (CSWS)
- High amplitude deltaactivity during Slow-Wave Sleep (SWS)
- Reduced SWS, but increased delta-activity in sleep
- Phasic chin muscle activity during rapid-eye-movement sleep (REMS) – REM sleep without atonia (RSWA)

- Electroencephalographic indices of auditory stimulus discrimination: decreased gamma-band oscillatory responses to familiar and novel voices
- Increased cortical excitability as determined by Transcranial Magnetic Stimulation (TMS)

Krajnc and Zidar. Eur J Paediatr Neurol. 2016 Jul;20(4):597-603
Bhat et al. J Child Neurol. 2014 Dec;29(12):NP176-80
Sarica et al. J Child Neurol. 2015 Feb; 30(2): 145–152.
Koyama et al. Brain Dev. 2001 Dec;23 Suppl 1:S104-7
Lv et al. BMC Neurol. 2016 Jun 13;16:9

Polysomnographic (PSG) findings in RTT

Polysomnography (PSG) studies have had conflicting results, with some indicating

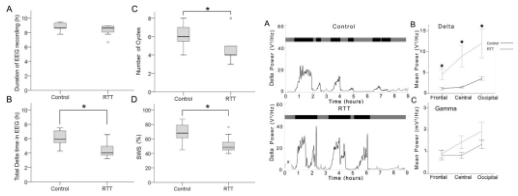
- relatively normal sleep architecture [1,2],
- while others reported increases [3] or decreases [4,5] in duration of rapid eye movement (REM) sleep

1. Polysomnographic characteristics of patients with Rett syndrome.*Marcus CL, Carroll JL, McColley SA, Loughlin GM, Curtis S, Pyzik P, Naidu S. J Pediatr. 1994 Aug; 125(2):218-24.*
2. Rett syndrome--clinical studies and pathophysiological consideration.*Nomura Y, Segawa M, Hasegawa M Brain Dev. 1984; 6(5):475-86.*
3. Rett syndrome--clinical studies and pathophysiological consideration.*Nomura Y, Segawa M, Hasegawa M Brain Dev. 1984; 6(5):475-86.*
4. Rett's syndrome: characterization of respiratory patterns and sleep.*Glaze DG, Frost JD Jr, Zoghbi HY, Percy AK Ann Neurol. 1987 Apr; 21(4):377-82.*
5. Polysomnographic findings in Rett syndrome: a case-control study. *Carotenuto M, Esposito M, D'Aniello A, Rippa CD, Precenzano F, Pascotto A, Bravaccio C, Elia M.Sleep Breath. 2013 Mar;17(1):93-8*

Electrophysiological abnormalities associated with poor outcome

Boxplot of EEG spectral analysis and sleep structure analysis.

Comparison of control EEGs' and RTT EEGs' delta power

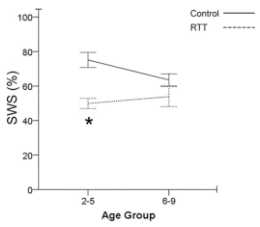


(A). Comparison of duration of overnight recordings in control EEGs with RTT EEGs revealed no significant differences. (B) Patients with RTT spent significantly less time during sleep in SWS (i.e.; high delta cycles) compared to the control group. (C) Patients with RTT had significantly fewer number of total SWS cycles compared to controls. (D) Therefore patients with RTT had significantly lower SWS percent

Ammanuel et al. PLoS One. 2015 Oct 7;10(10):e0138113

SWS percent in Age Group

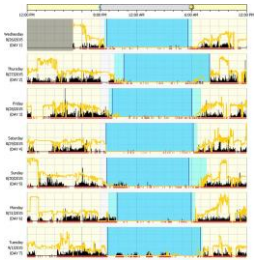
- SWS is diminished in RTT, but difference is reduced by age 6-9.
- This could – however – be explained by increased occurence of delta-activity by advanced disease.
- REM sleep were not recorded in this study



Ammanuel et al. PLoS One. 2015 Oct 7;10(10):e0138113

Circadian/sleep efficiency studies in RTT (actigraphy)

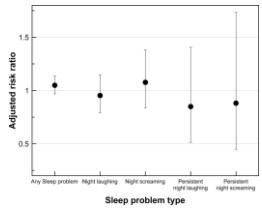
- Normal sleep-wake rhytmicity
- Almost all (N=13) showed normal total sleep time (492 mins) but reduced sleep efficiency especially among those with uncontrolled seizures/epilepsy



Merbler et al. J Neurodev Disord. 2018; 10: 8

Effect of specific sleep medication (compared to no treatment) on the likelihood of unresolved sleep problem by sleep problem type

- Open design
- Evaluated drugs: melatonin, clonidine, trimeprazine, amitriptyline, respidone, promethazine, others



Disturbance of phasic chin muscle activity during rapid-eye-movement sleep

- Disturbance in phasic chin muscle activity during rapid-eye-movement sleep (REMS): REM sleep without atonia
- Observed in RETT syndrome, infantile spasms, severe myoclonic epilepsy in infancy (SMEI), severe nocturnal enuresis, and autism [(1)].
- Commonly observed in adult patients with Parkinson's disease (PD), hypocretin deficient narcolepsy and REM sleep Behavior Disorder[(2)]
- Due to involvement of subceroleus (sublatoro-dorsal nucleus) in the pontine region[(2)]

Koyama et al. Brain Dev. 2001 Dec;23 Suppl 1:S104-7
Jennum et al. Nat Sci Sleep. 2016 Apr 15;8:107-20

Sleep disordered breathing

- RTT patients may show higher degree of sleep apnea (including central sleep apnea) and hypoventilation
- May also be associated with CDKL5 gene mutation
- Males with MECP2 mutations may show respiratory failure resempling Ondine syndrome.
- Suggest a failure of brainstem respiratory centres to control respiration
- In addition REM sleep may show reduction
- However, in many RTT patients nocturnal saturation are normal.

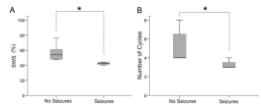
Hegebeuk et al. Dev Med Child Neurol. 2013 May;55(5):480-4
Carotenuto et al. Sleep Breath. 2013 Mar;17(1):93-8
Gallego J. Compr Physiol. 2012 Jul;2(3):2255-79
Falsaperla et al Eur J Paediatr Neurol. 2012 Nov;16(6):744-8
D'Orsi et al. Neurol Sci. 2009 Oct;30(5):389-91

Sleep and epilepsy

Seizures correlates with high delta power and lower SWS

Clinical severity of patients with RTT were recorded and documented. Seizures are a characteristic of RTT. Patients with RTT were separated into two groups: patients who showed no seizures and patients who experienced seizures

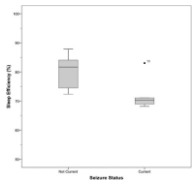
- (A) Patients with RTT who experienced seizures correlated negatively with lower SWS percent.
- (B) In addition patients with RTT who experienced seizures correlated negatively with lower cycles during sleep.



Ammanuel et al. PLoS One. 2015 Oct 7;10(10):e0138113

Sleep efficiency and seizures

Actigraphy-derived sleep efficiency was significantly lower among those whose parents reported that they had seizures that were not controlled by medications at the time of the study (N = 5, M = 72.32%, SD = 6.10), compared to those with no history of seizures and those whose seizures were well controlled (N = 7, M = 79.05%, SD = 6.37)



Merbler et al. J Neurodev Disord. 2018; 10: 8

Clapping-surpressed focal spikes in EEG may be unique for the patients with rett syndrome : a case report.

Continuous centrotemporal spikes in the EEG, and clapping-supressed focal spikes in EEG

- Female, 4 years old, presented with a significant regression in her spoken language skills, hand stereotypies (hand clapping and hand wringing), a wider based gait with difficulties in balance, repeated abnormal behaviors (bruxism and head banging)
- EEG showed slow acticity in background and revealed a specific feature that continuous centrotemporal spikes can be suppressed by the repeated hand clapping

Lv et al. BMC Neurol. 2016 Jun 13;16:9

Epilepsy and RTT

- Affects 50-90%
- Early onset
- Often dyskinetic movements.
- Associated with significant comorbidity
- Often refractory to medical treatment
- Often requiring polypharmacology and non pharmacological treatment (e.g. ketogenic diet, vagus stimulation)
- Some AED (topiramate) may interphere with respiration

Dolce et al. Pediatr Neurol. 2013 May;48(5):337-45
Krajnc N. J Child Neurol. 2014 Oct;29(10):NP118-21

Evoked potentials

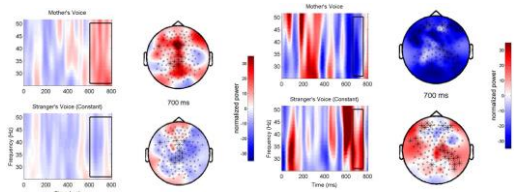
Generally: all modalities show abnormalities associated with cognitive and disease progression impairment, suggesting general involvement of multiple brain areas including brain stem:

- Visual Evoked Potential (VEP): impaired responses including abnormal respose to increased spatial frequency
- Event-related potentials (ERP): longer ERP latencies and smaller ERP amplitudes suggesting slowed information processing and reduced brain activation
- Somatosensory-evoked potentials (SEP): "giant" responses, suggesting cortical hyper-excitability
- Transcranial Magnetic Stimulation: abnormal excitatory and inhibitory motor responses
- These data underly significant influence brainstem, midbrain and cortical network as expressed by abnormal excitation/inhibition.

LeBlanc et al. Ann Neurol.2015 Nov;78(5):775-86
Krajnc & Zidar. Eur J Paediatr Neurol. 2016 Jul;20(4):597-603
Stauder et al. Brain Dev.2006 Sep;28(8):487-94
Glaze DG. Ment Retard Dev Disabil Res Rev. 2002;8(2):66-71

Induced gamma oscillations differentiate familiar and novel voices in children with *MECP2* Duplication and Rett syndromes

MECP2* Duplication** ***RTT



Gamma-band oscillatory activity, since abnormalities in gamma activity are thought to reflect deficits in excitatory-inhibitory balance, and are associated with coordination of neural activity15, 18 and support of higher-order cognitive processes such as attention and memory, including acoustic/auditory object representation

Sarica et al. J Child Neurol. 2015 Feb; 30(2): 145–152.

Summary

- Sleep and wake are under complex homeostatic and circadian regulation
- This is regulated by several nuclei in brainstem, mid- and forebrain
- Patients with Rett syndrome present multiple abnormalities especially in sleep regulation causing severa sleep problems (insomnia, sleep fragmentation, abnormal behavior, breathing abnormalities, seizures) and multiple associated electrophysiological abnormalities.
- This suggest that the wake-sleep regulatory systems are involved in disease and its advancement.