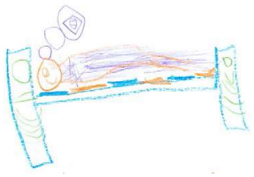


The complicated relationship between sleep, epilepsy and antiepileptics in Children

J Helen Cross

UCL-Great Ormond Street Institute of Child Health, London, & Young Epilepsy, Lingfield, UK

Outline

- Epilepsy and cognition
- The relationship between sleep and epilepsy
- Normal sleep development
- Sleep epilepsy and antiepileptics
- Sleep and cognition
- Sleep, epilepsy, and cognition

Natural History?

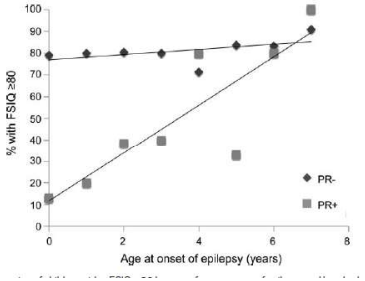
Cognitive deficits progress over time

Longitudinal study of a cohort with epilepsy onset < 3 years

TABLE 1. Mean Vineland Scores at Initial Study Entry and Over Time for the Full Study Sample (n = 172)

Domain	Baseline, Mean (SE)	1 Year, Mean (SE)	2 Years, Mean (SE)	3 Years, Mean (SE)	P Value for Trend
Composite	92.0 (1.5)	86.6 (2.0)	82.9 (2.4)	81.5 (2.7)	<.0001
Communication	93.4 (1.5)	90.4 (2.0)	87.2 (2.0)	85.2 (2.3)	.0003
Daily Living	89.6 (1.4)	79.0 (1.6)	76.5 (2.0)	74.6 (2.4)	<.0001
Motor	94.4 (1.7)	90.0 (2.2)	83.1 (2.5)	80.5 (3.3)	<.0001
Social	96.1 (1.7)	92.7 (2.0)	90.0 (2.2)	88.8 (2.4)	.0015

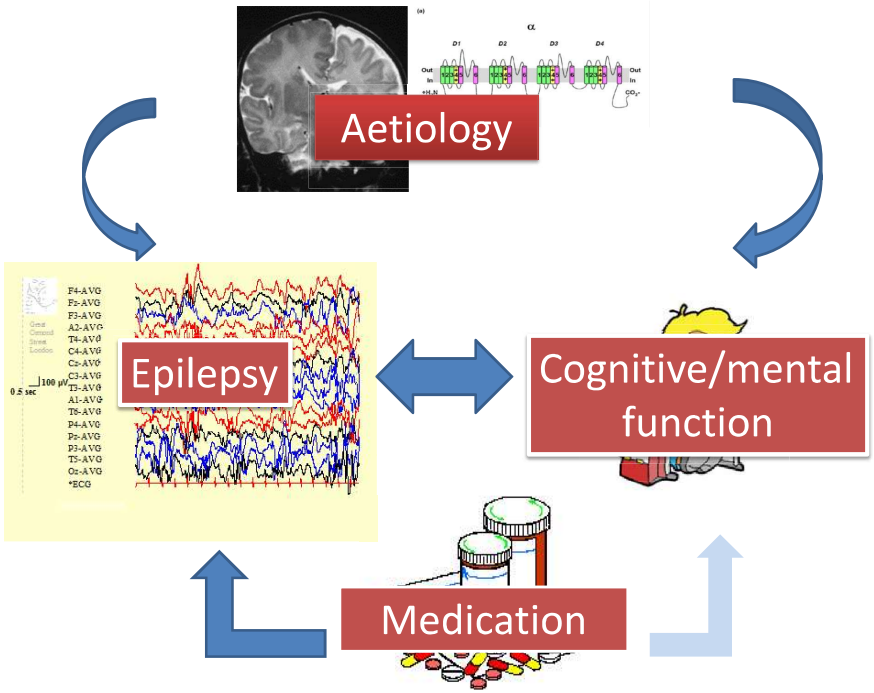
Berg et al Pediatrics 2004;114: 645-650



Longitudinal study to 8-9 years following seizure onset <8 years

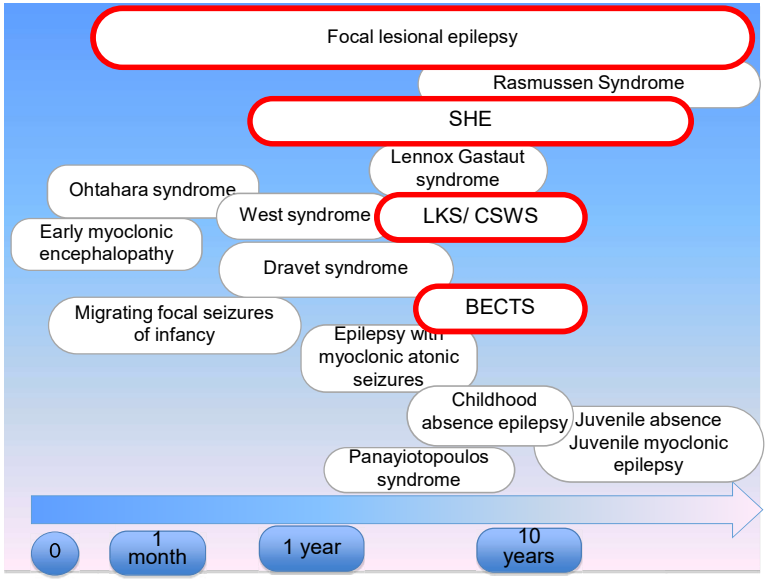
Dichotomous IQ indicator strongly correlated with age at onset in pharmacoresistant group (p<0.0001) , not pharmacoresponsive group (p=0.61)

Berg et al Neurology 2012;79:1384-1391



Sleep and epilepsy

Sleep related epilepsy syndromes



Frontal lobe seizures- characteristics

- Nocturnal preponderance
- Rapid secondary generalisation
- Focal clonic motor activity without march
- Prominent asymmetric tonic posturing
- Complex, bizarre motor automatisms
- Explosive onset-sudden end
- Minimal post ictal confusion
- Frequent, brief seizures
- Clusters
- Status epilepticus of all types
- Prominent mood changes
- Bizzarre hysterical appearance
- Vocalisation

Autosomal Dominant Nocturnal Frontal Lobe Epilepsy

- Onset childhood or adolescence
- Stereotyped motor seizures from sleep, retained awareness, often feeling of shortage of breath
  - Normal intelligence
  - Normal EEG
  - MRI normal
- Associated with loss of function mutations in the α2, α4, or β2 subunits of the ligand gated neuronal nicotinic acetylcholine receptor (nAChR) in some families
- Usually respond to carbamazepine

Epilepsy & Behavior 17 (2010) 531–535

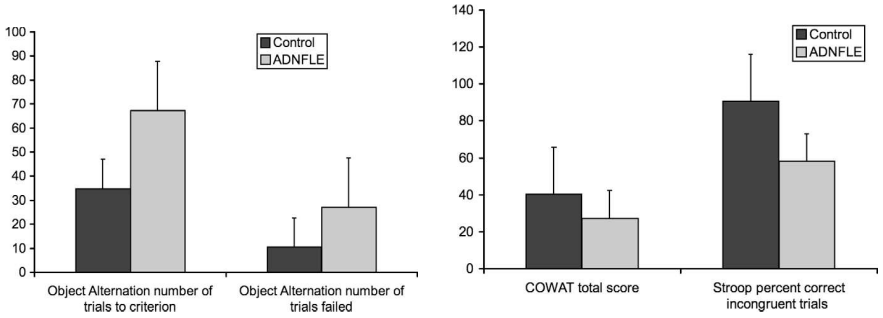
Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Neuropsychological function in patients with a single gene mutation associated with autosomal dominant nocturnal frontal lobe epilepsy

Amanda G. Wood [a,b,*], Michael M. Saling [c,d], Marco Fedi [e], Samuel F. Berkovic [e], Ingrid E. Scheffer [e,f], Christopher Benjamin [a], David C. Reutens [a,g]



VIEWS & REVIEWS

Definition and diagnostic criteria of sleep-related hypermotor epilepsy

OPEN

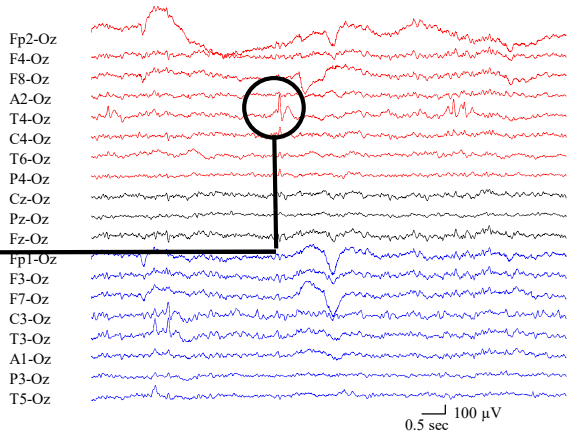
Paolo Tinuper, MD
Francesca Bisulli, MD, PhD
J.H. Cross, MD, PhD
Dale Hesdorffer, PhD
Philippe Kahane, MD, PhD
Lino Nobili, MD, PhD
Federica Provini, MD, PhD
Ingrid E. Scheffer, PhD, MBBS
Laura Tassi, MD
Luca Vignatelli, MD, PhD
Claudio Bassetti, MD
Fabio Cirignotta, MD
Christopher Derry, PhD
Antonio Gambardella, MD
Renzo Guerrini, MD
Peter Halasz, MD, PhD
Laura Licchetta, MD
Mark Mahowald, MD
Raffaele Manni, MD
Carla Marini, MD, PhD
Barbara Mostacci, MD, PhD
Ilaria Naldi, MD, PhD
Liborio Parrino, MD, PhD
Fabienne Picard, MD
Maura Pugliatti, MD, PhD
Philippe Ryvlin, MD, PhD
Federico Vigevano, MD
Marco Zucconi, MD
Samuel Berkovic, MD, FRS*
Ruth Ottman, PhD*

Tinuper et al Neurology 2016

- **characterized by the occurrence of brief (,2 minutes) seizures with stereotyped motor patterns within individuals and abrupt onset and offset**
- **The most common clinical expression consists of "hypermotor" events.**
- **Seizures of SHE occur predominantly during sleep; however, seizures during wakefulness may also occur**

Benign Epilepsy with Centrotemporal Spikes

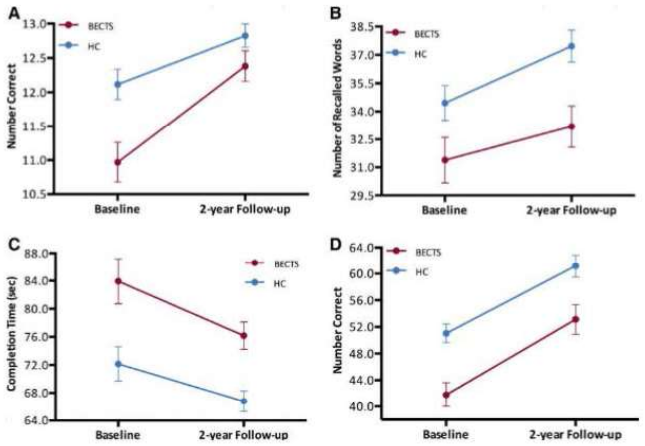
- **Age 5-10 years**
- **Seizures from sleep**
  - **Rolandic 'focal motor'**
  - **GTC**
- **Centrotemporal spikes on EEG**
- **To treat or not to treat?**



Cognition and brain development in children with benign epilepsy with centrotemporal spikes

*Camille Garcia-Ramos, †Daren C. Jackson, ‡Jack J. Lin, †Kevin Dabbs, †Jana E. Jones, †David A. Hsu, §Carl E. Stafstrom, †Lucy Zawadzki, ¶Michael Seidenberg, #Vivek Prabhakaran, and †Bruce P. Hermann

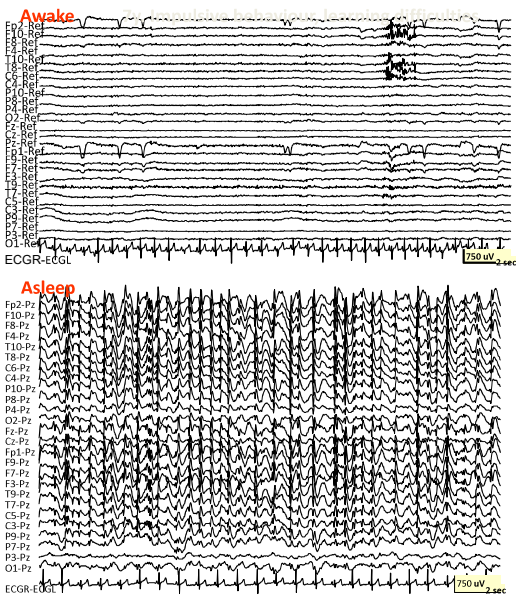
Epilepsia, 56(10):1615–1622, 2015
doi: 10.1111/epi.13125



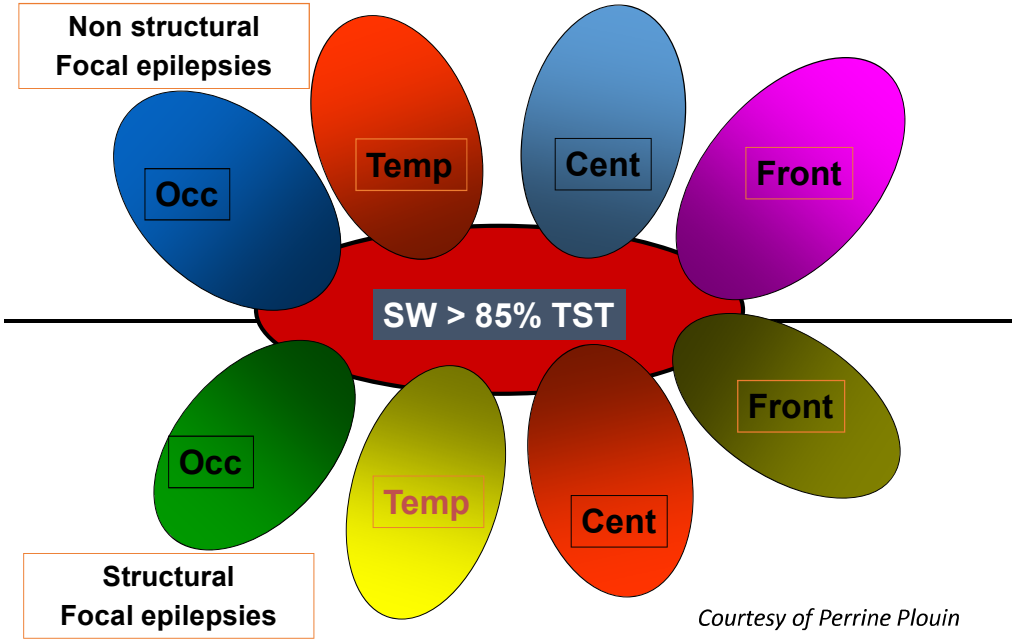
Epilepsia, 56(10):1615–1622, 2015
doi: 10.1111/epi.13125

Continuous Spike Wave of Slow Sleep

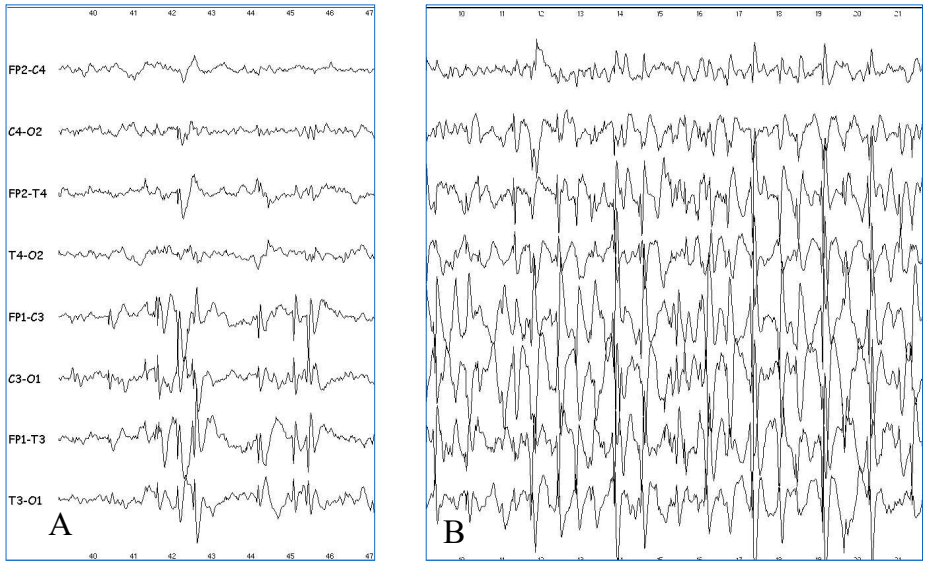
- **Neuropsychological and behavioural change temporally related to the presence of almost continuous spike wave activity on EEG in sleep.**
- **First described by Patry Lyagoubi and Tassinari 1971**



Continuous Spike and Waves during Slow Sleep



Courtesy of Perrine Plouin



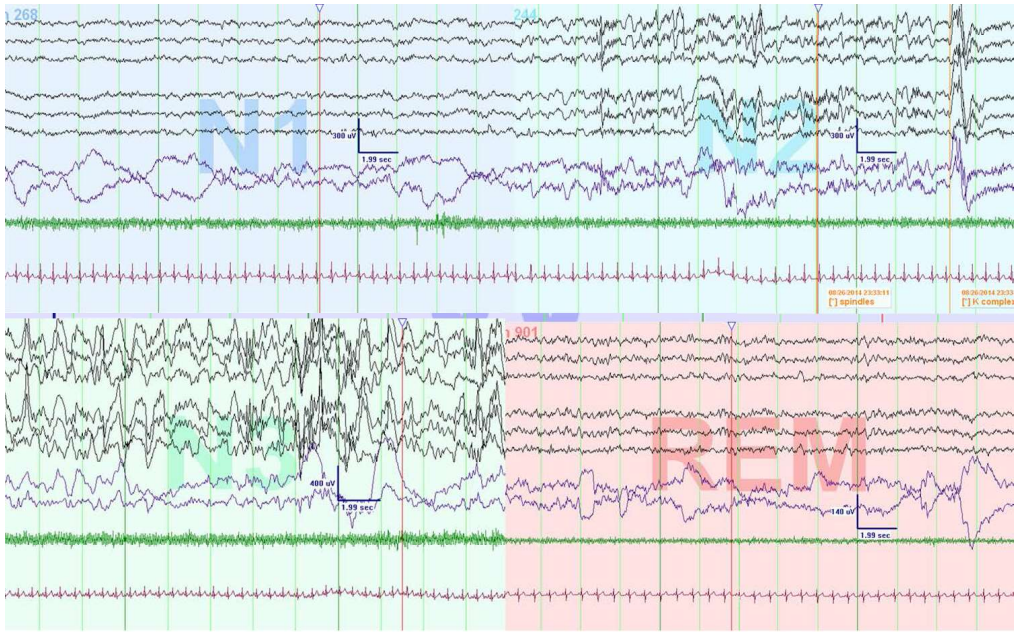
Landau-Kleffner syndrome

CSWS fronto-central focus

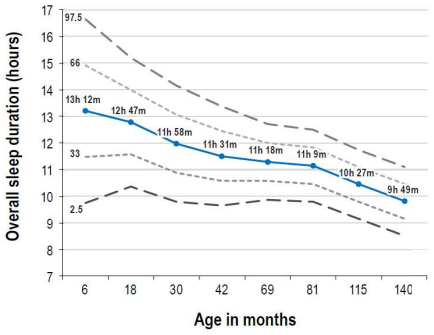
Sleep development

Sleep regulation

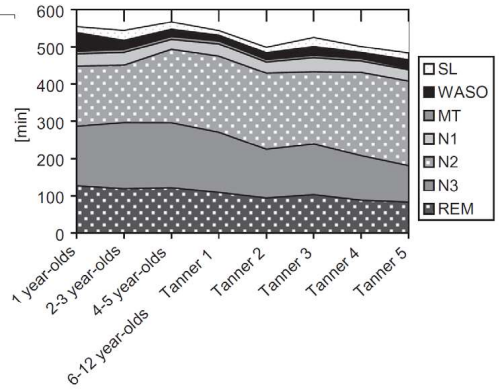
Neurotransmitter	Wake	REM	NREM
Acetylcholine	high	high	low
Serotonin	high	none	low
Dopamine	high	high	low
Norepinephrine	high	none	low
Histamine	high	none	low
GABA	none	low	high
Orexin	high	none	none
MCH	low	high	low



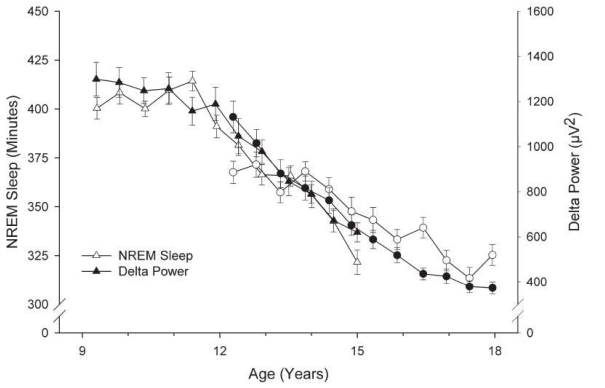
Change in sleep patterns over childhood



Adapted from Blair 2012

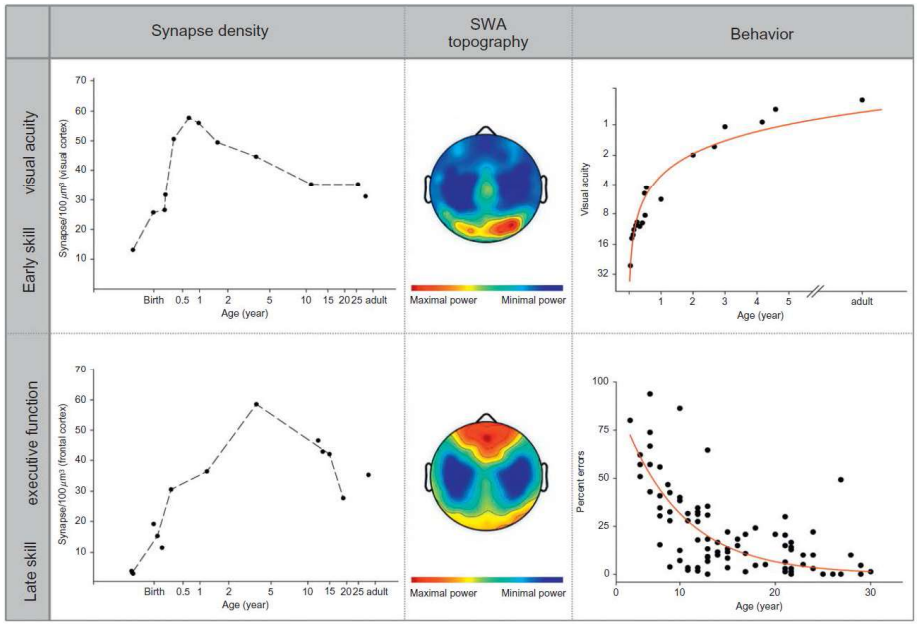


Adapted from Scholle 2011



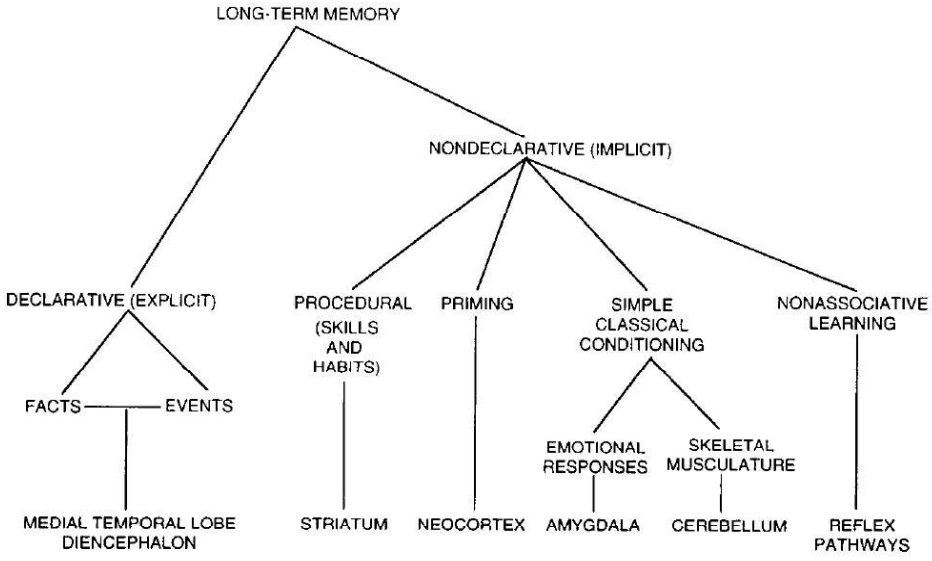
AJP-Regul Integr Comp Physiol • doi:10.1152/ajpregu.00532.2011

Feinberg et al. 2011



Ringli and Huber 2011

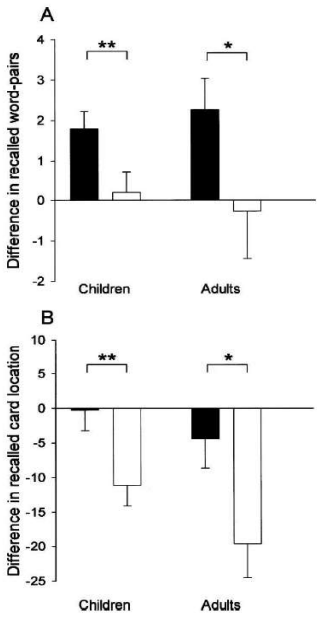
Sleep and cognition



Squire and Zola (1996)

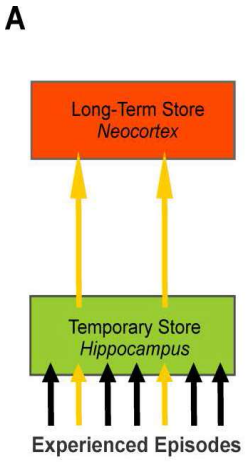
Is sleep necessary for cognitive function and intellectual development?

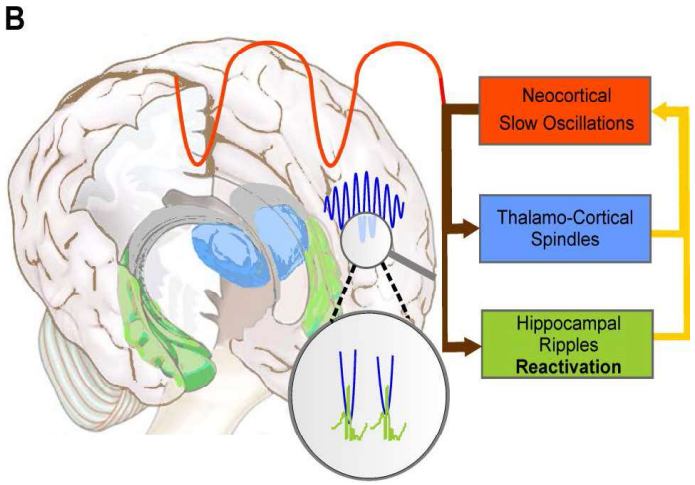
- **The same neuronal networks are used for both the processing and the long-term storage of information**
- **Maturational changes in the cortex occur in tandem with the maturation of sleep**



Wilhelm and Diekelmann 2008

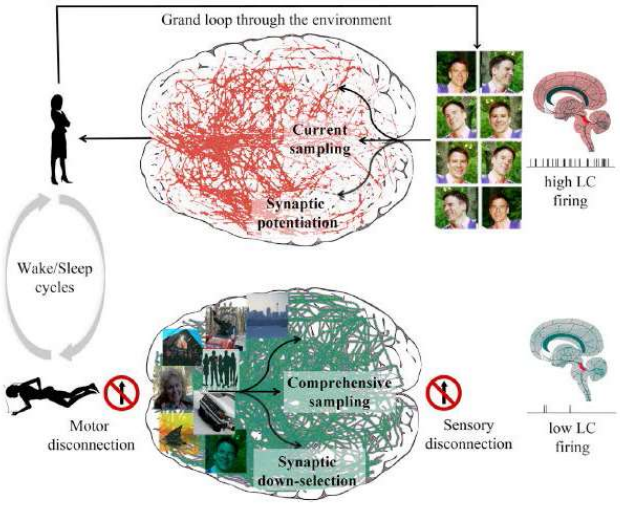
Active system consolidation



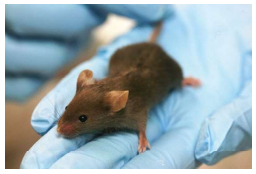


Mölle and Born *Prog Brain Res* 2011

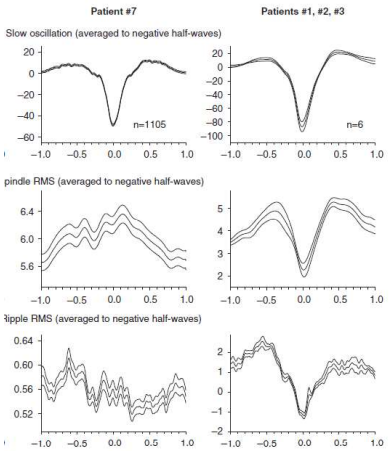
Synaptic homeostasis



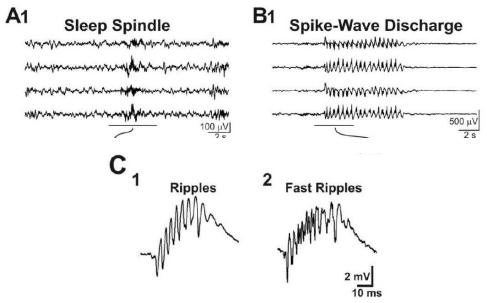
Tononi and Cirelli *Neuron* 2014



Sleep, epilepsy and cognition



Clemens 2007



Beenhakker 2009

Role of anti-epileptic drugs

	N1	N2	N3/SWS	REM	WASO/ arousals
Levetiracetam	↔	↑	Conflicting data	↓	↓
Pregabalin	↓	↔	↑	↔	↓
Clobazam	↓	↑	↓	↔	↓
Gabapentin	↓	↔	↑	Conflicting data	↓
Tiagabine	↔	↔	↑	↓	↓
Phenobarbitone	↔	↑	↔	↓	↓
Carbamazepine		↔	↑	↓	↓
Ethosuximide	↑	↔	↓	↑	↔
Phenytoin	↑	↑	Conflicting data	↓	↔

Jain & Glauser 2014

Epilepsy & Behavior 63 (2016) 57–62

Contents lists available at ScienceDirect

Epilepsy & Behavior

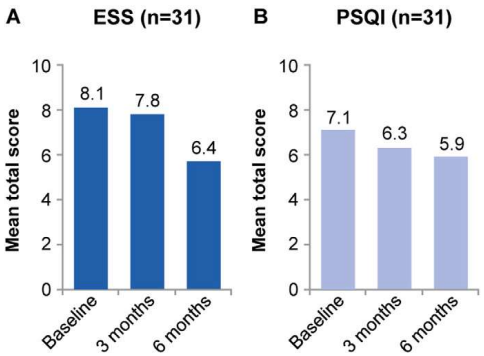
journal homepage: www.elsevier.com/locate/yebeh

Sleep quality and daytime sleepiness in patients treated with adjunctive perampanel for focal seizures

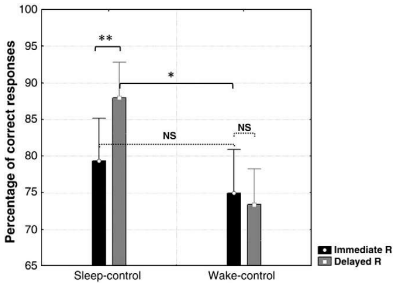
Manuel Toledo [a,*], Montserrat Gonzalez-Cuevas [a], Julia Miró-Lladó [b], Albert Molins-Albanell [c], Mercé Falip [b], Ana Belén Martinez [d], Santiago Fernandez [e], Manuel Quintana [a], Roser Cambrodi [f], Estevo Santamarina [a], Javier Salas-Puig [a]

72 patients, drug resistant focal seizures

- **mean baseline PSQI score 7.26 (±4.6), and ESS 6.19 (±4.2).**
- **3 months (median perampanel dose: 4 mg), no significant change in ESS score (n=61); significant improvement in PSQI (−1.51 points; n=44; p = 0.007),**



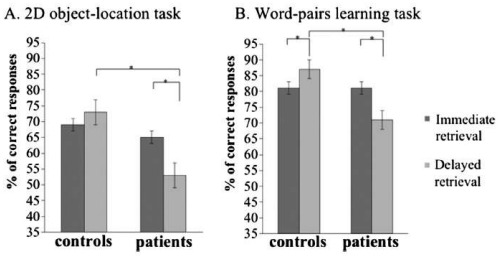
Epilepsy & Cognition – the role of sleep



	Session 1		Session 2		Session 3	
	Immediate R	Delayed R	Immediate R	Delayed R	Immediate R	Delayed R
Controls (SD)[a]	79.30 (11.35)	87.91 (8.01)	78.60 (8.19)	86.94 (7.58)	84.30 (10.16)	92.63 (5.38)
Patient 1[a]	66.66	56.66				
p-value[b]	0.003					
Patient 2[a]	100.0	70.00				
p-value[b]	<0.001					
Patient 3[a]	80.00	60.00	96.66	83.33	76.92	84.61
p-value[b]	<0.001		<0.001		0.20	
Patient 4[a]	75.00	65.00	83.33	72.22	61.53	53.84
p-value[b]	0.005		<0.001		<0.001	

R = retrieval; SD = standard deviation.
[a] Percentage of correct responses.
[b] Crawford's analysis assessing significance of immediate vs. delayed retrieval performance in each patient's session as compared to changes in control group.

Urbain et al Epilepsy Behav 2011;22:380-384



S. Galer et al. / Epilepsy & Behavior 43 (2015) 16–23

- **15 patients with IFS, 3 without epilepsy**
- **8 healthy controls**
- **No control condition (i.e. interval without sleep for comparison)**

Clinical Neurophysiology 122 (2011) 1779–1787

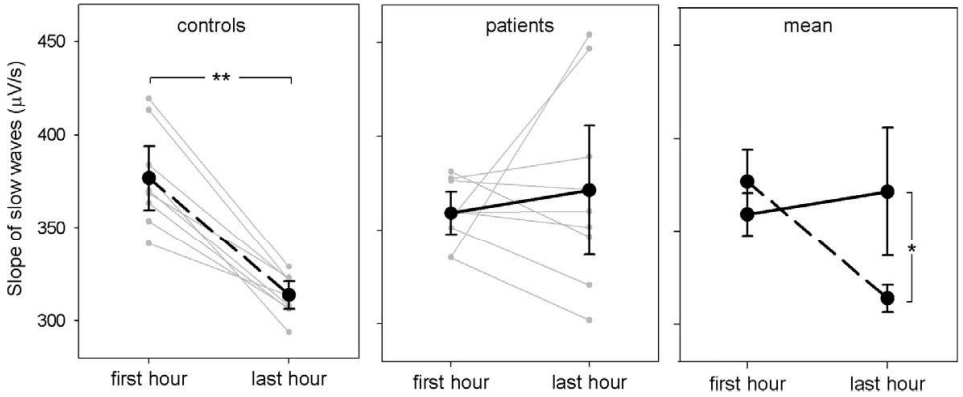
Contents lists available at ScienceDirect

Clinical Neurophysiology

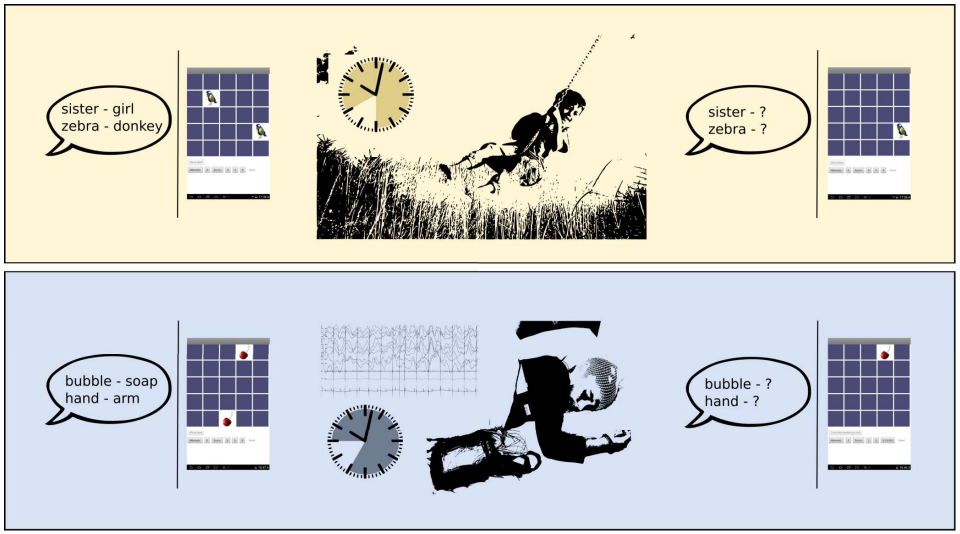
journal homepage: www.elsevier.com/locate/clinph

Impaired slow wave sleep downscaling in encephalopathy with status epilepticus during sleep (ESES)

Bigna K. Bölsterli [a], Bernhard Schmitt [a], Thomas Bast [b,c], Hanne Critelli [a], Jakob Heinzle [d], Oskar G. Jenni [e], Reto Huber [e,*]

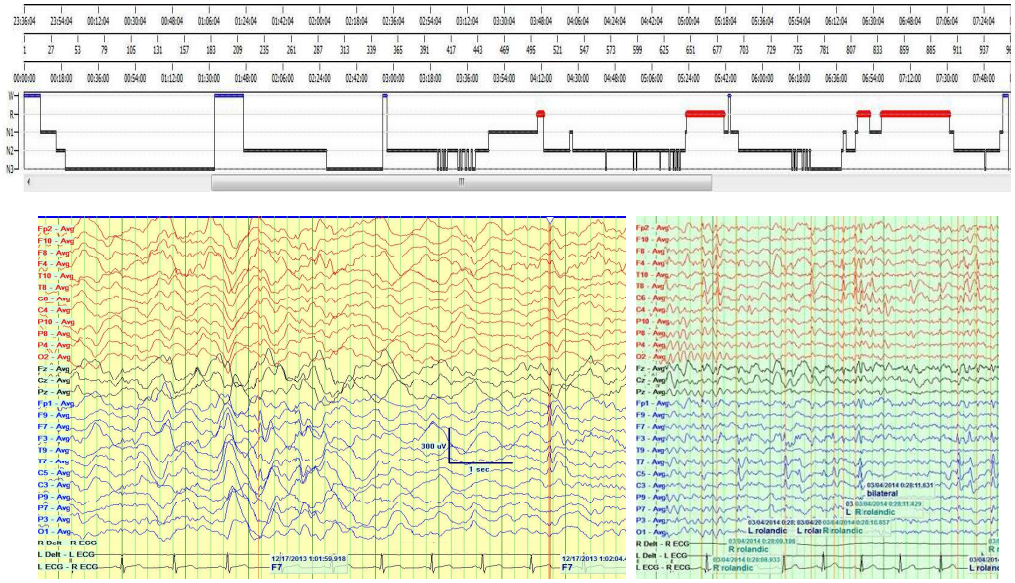


Memory consolidation in sleep – a paradigm



Chan et al. Epilepsia 2017

Sleep staging and discharge counting

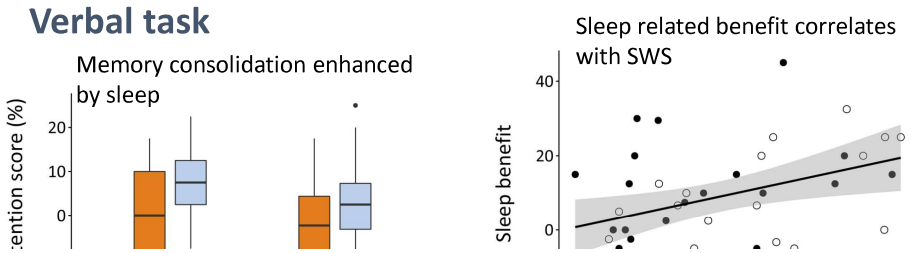


Participants

	Patients (n=22)	Controls (n=21)	p
Descriptive statistics			
Age (years)	11.5 (+/-3.0)	10.6(+/-2.8)	0.34
Sex (females, males)	8, 14	12, 9	0.18
FSIQ	88.4(+/-11.3)	115.3(+/-12.9)	<0.001
Epilepsy characteristics			
Age of seizure onset (years)	5.3(+/-4.1)		
Duration of seizures (years)	6.1(+/-2.8)		
MRI findings			
No lesion	32%		
Focal cortical dysplasia	32%		
Mesial temporal sclerosis	9%		
Low grade tumour	9%		
Other lesion	18%		
Seizure frequency			
Daily	22%		
Weekly	41%		
Monthly	14%		
<1 per month	23%		
Seizure localisation			
Frontal	13%		
Temporal	27%		
Fronto-temporal	23%		
Central	5%		
Parietal	5%		
Undetermined	27%		

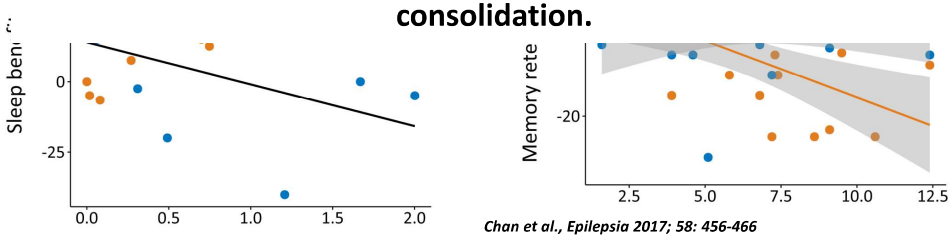
Sleep quality

- **Patients had worse sleep habits on CSHQ (p=<0.001)**
- **During the ‘sleep’ interval, patients slept less than controls (p=0.002), and the deficit was in N3 (p=0.04) and REM (p<0.001), rather than light sleep (p>0.6 for both N1 and N2).**
- **Five patients had seizures during the ‘sleep’ interval while 2 had seizures during the ‘wake’ interval**



sleep-related memory consolidation may serve as a compensatory mechanism to maintain cognitive function

in agreement with predictions, a higher interictal discharge load during sleep was associated with a lesser contribution of sleep to memory consolidation.



Chan et al., Epilepsia 2017; 58: 456-466

Summary

- **Complex relationship between sleep, epilepsy and cognition**
- **Compounded by antiepileptic drugs**
- **sleep-related memory consolidation may serve as a compensatory mechanism to maintain cognitive function**
- **?role for duration/increasing slow wave sleep**