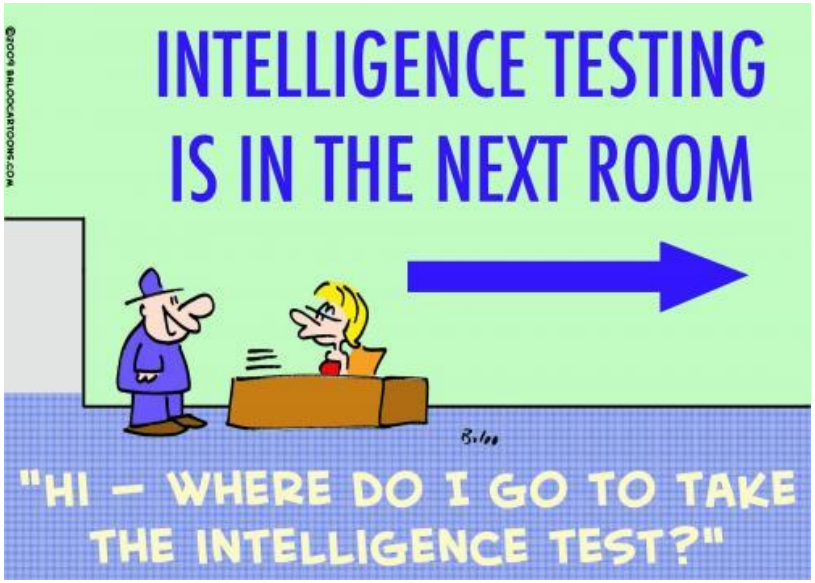


Cognitive issues in childhood epilepsy

Lieven Lagae

Paediatric Neurology

University Hospitals KULeuven Belgium

Cognitive and behavioral problems are *frequent* in *refractory* childhood epilepsy

	NORMAL IQ	>70	50 – 70	35 – 49	20 – 34	< 20	Unknown
With behavioural problems (461)	73	75	101	68	54	64	26
	15,8 %	16,3 %	22 %	14,8 %	11,7 %	13,9 %	5,6 %
Without behavioural problems (112)	18	10	16	17	25	19	7
	16,1 %	8,9 %	14,3 %	15,2 %	22,3 %	16,9 %	6,25 %

Epilepsy Centre Pulderbos, Belgium

Neuropsychology: Cognitive Domains

- Sensory processing / perception
- Attention / concentration
- Speed of processing
- Working memory
- Psychomotor speed

cognitive instruments

- Visuospatial abilities
- Problem-solving
- Non-verbal memory
- Verbal memory
- Motor control / performance
- Verbal reasoning
- Imagery

'specific' processes

- General intelligence , IQ

'overall cognitive ability'

Lagae L, *Seizure* 2006

Model

Etiology, epilepsy syndrome

cumulative effect seizures and EEG abnormalities

Effect on **stable aspects** of cognitive functions:

→ learning, memory, academic achievement, IQ

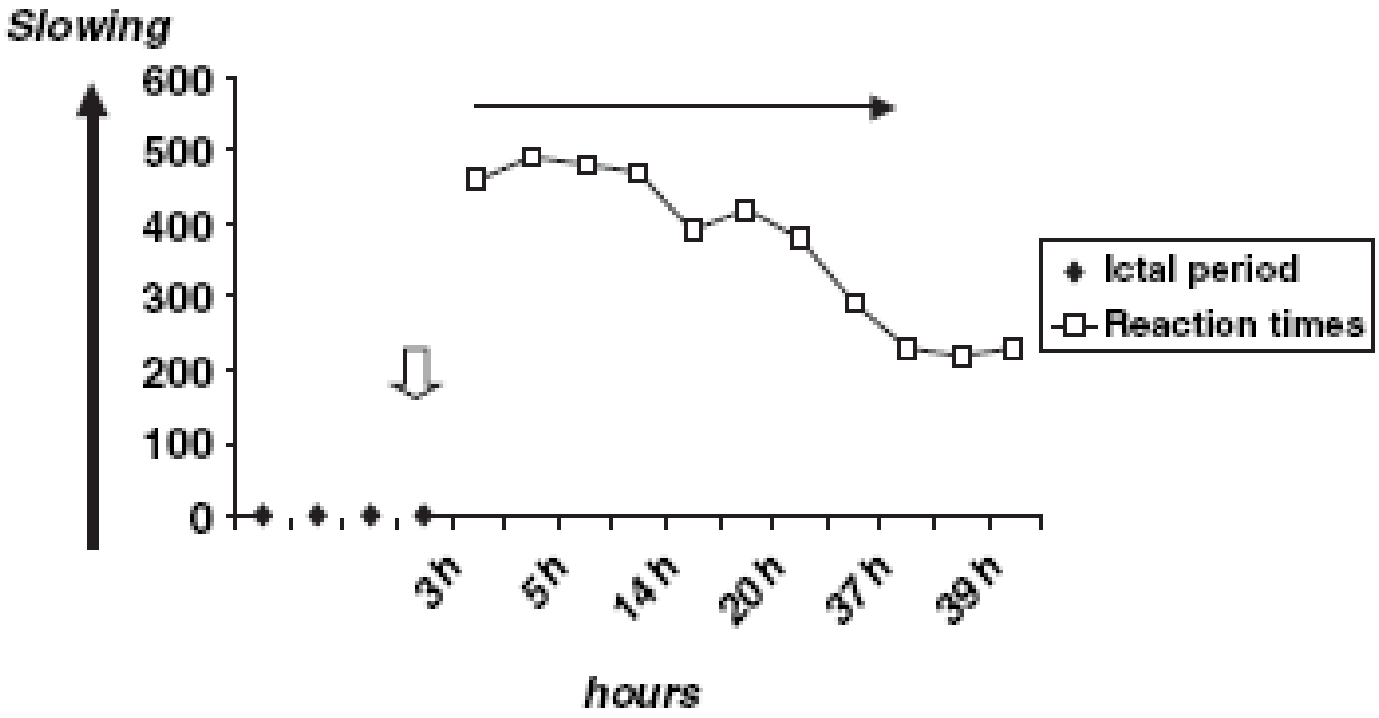
Epileptic EEG activity, medication, acute seizures

Effect on **transient aspects** of cognitive functions:

→ attention, reaction time, processing speed

Aldenkamp and Arends, *Epilepsia* 2004

Effect of 1 GTC seizure on reaction time



Aldenkamp and Bodde, Acta Neurol Scand 2005, 112:19-25

Cognitive dysfunctions in childhood epilepsy

Underlying etiology (structural, genetic,...)

Seizure type, localization

Seizure frequency, severity

Epilepsy syndrome

EEG abnormalities

Seizure control

Treatment – antiepileptic drugs (AEDs)

Psychosocial environment

How important is each factor ?

Cognitive dysfunctions in childhood epilepsy

Underlying etiology (structural, genetic,...)

Seizure type, localization

Seizure frequency, severity

Epilepsy syndrome

EEG abnormalities

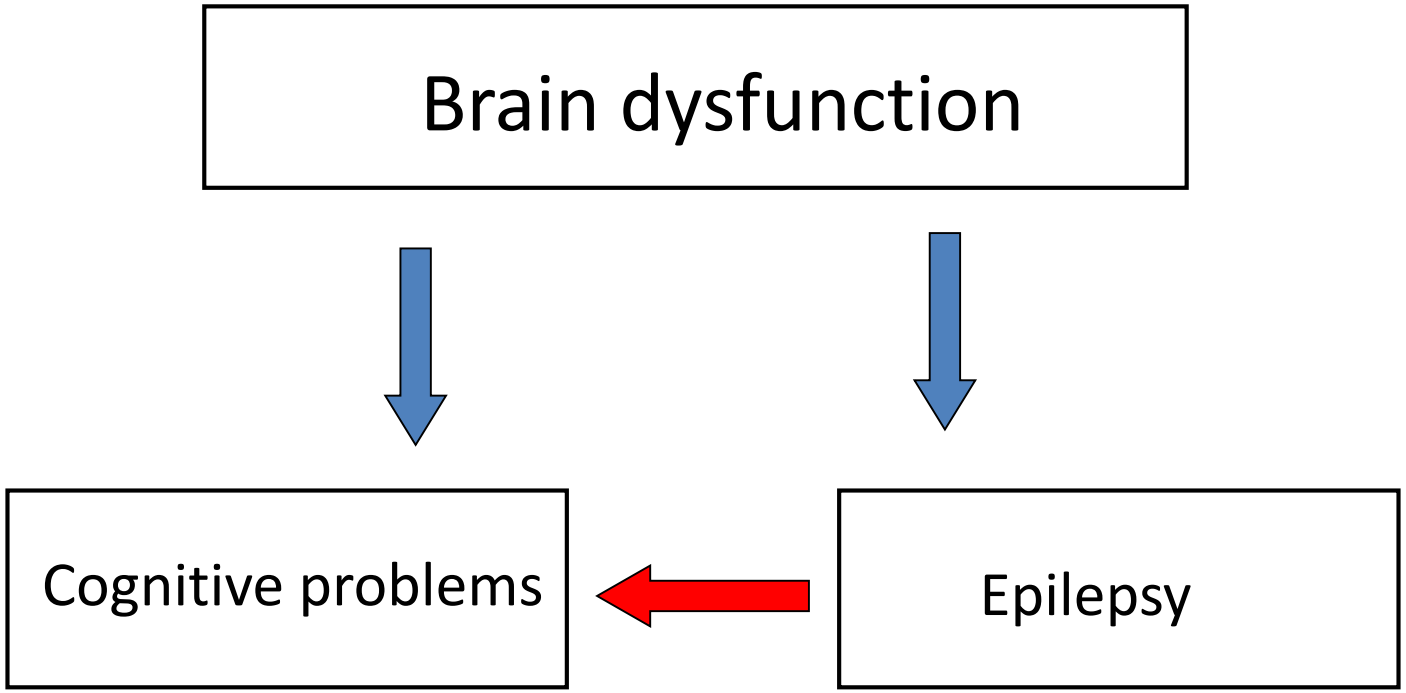
Seizure control

Treatment – antiepileptic drugs (AEDs)

Psychosocial environment

Etiology ?

Cognitive problems at the onset of childhood epilepsy



THE JOURNAL OF PEDIATRICS • www.jpeds.com

The Neuropsychological and Academic Substrate of New/Recent-Onset Epilepsies

Daren C. Jackson, PhD[1], Kevin Dabbs, MS[1], Natalie M. Walker, BS[1], Jana E. Jones, PhD[1], David A. Hsu, MD, PhD[1], Carl E. Stafstrom, MD, PhD[1], Michael Seidenberg, PhD[2], and Bruce P. Hermann, PhD[1]

Table I. Characteristics of controls and epilepsy participants by subsyndrome (mean and SD)

Variable	Healthy controls (n = 72)	BECTS (n = 22)	Focal (n = 31)	JME (n = 26)	Absence (n = 11)
Age (y)	12.86 (3.20)	10.25 (1.40)	11.82 (2.94)	14.62 (3.06)	12.24 (3.46)
Sex (number/% female)	37 (51%)	10 (44%)	14 (45%)	14 (54%)	4 (36%)
FSIQ	107.35 (12.00)	103.00 (14.53)	98.52 (10.90)	101.62 (13.89)	98.18 (11.16)
AP(+/−)	13/58	15/8	16/15	12/14	5/6
Age of seizure onset (y)	-	9.00 (2.41)	10.51 (2.81)	13.21 (4.09)	11.20 (3.52)
Seizure frequency (<1 y, >1 y)	-	4/19	4/27	7/19	3/8
Epilepsy duration (mo)	-	7.22 (4.04)	8.26 (3.56)	8.46 (3.49)	9.73 (3.17)
Antiepileptic drugs (0/1/2+)	-	9/14/0	6/24/1	0/25/1	0/9/2

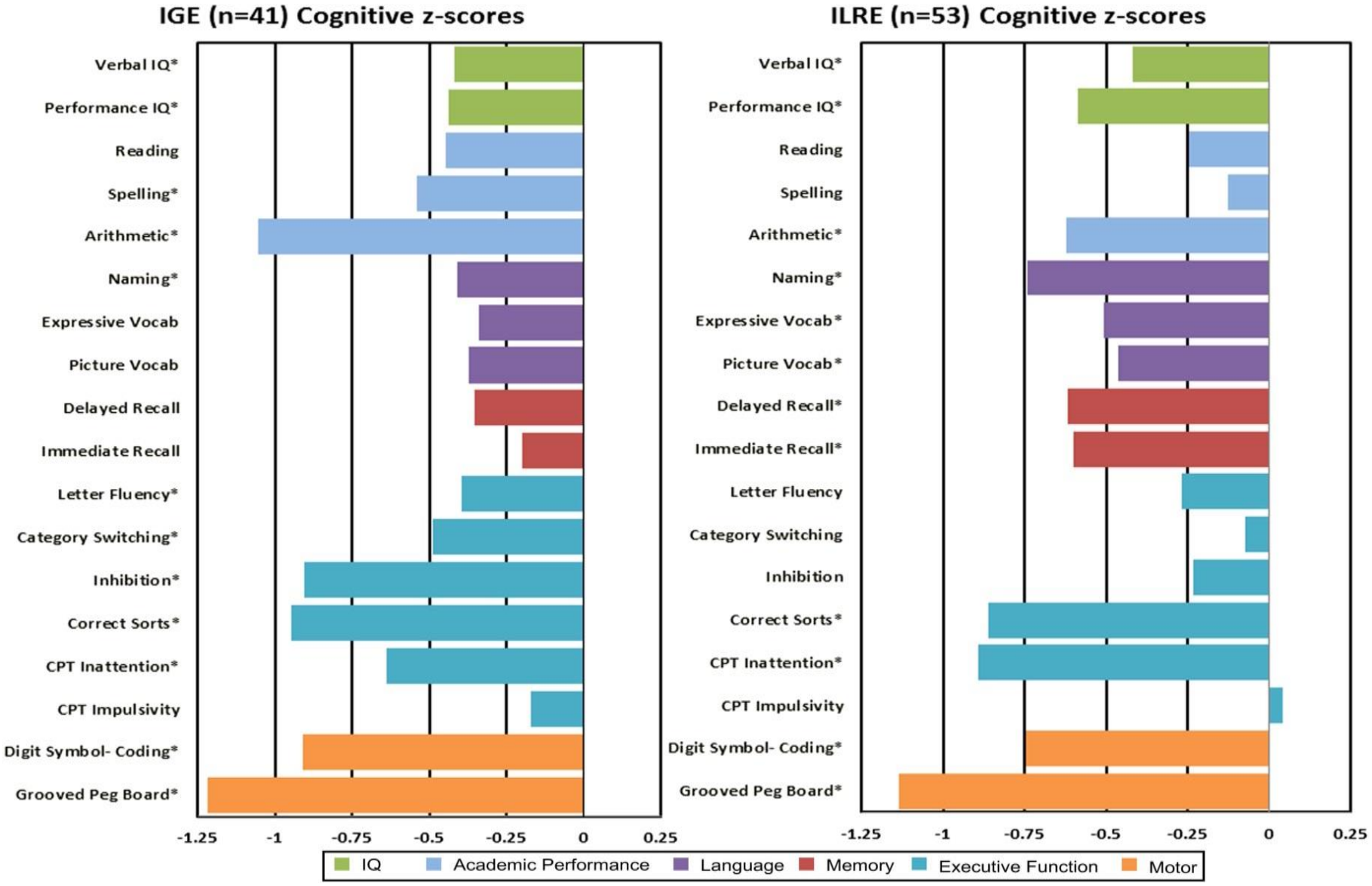


Figure 1 Cognitive performance by major epilepsy syndrome (IGE, ILRE). All scores have been age- and sex-corrected relative to controls, and are plotted here with z-scores relative to controls. Asterisks denote P values <.05. CPT , continuous perform...

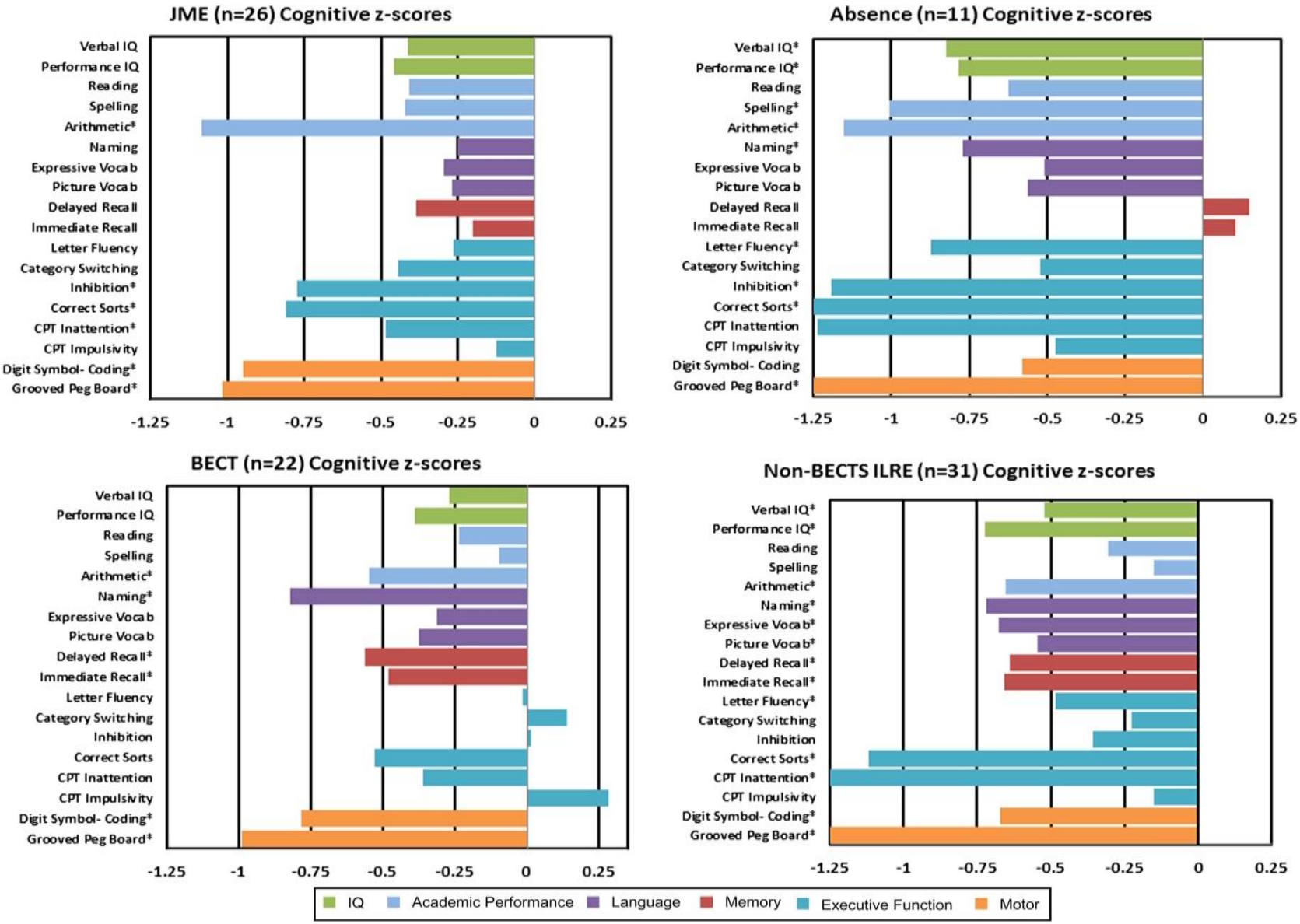


Figure 2 Cognitive performance by epilepsy subsyndrome (BECTS, Absence, JME, Focal). All scores have been age- and sex-corrected relative to controls, and are plotted here with z-scores relative to controls. Asterisks denote P values <.05.

Cognitive dysfunctions in childhood epilepsy

Underlying etiology (structural, genetic,...)

Seizure type, localization

Seizure frequency, severity

Epilepsy syndrome

EEG abnormalities

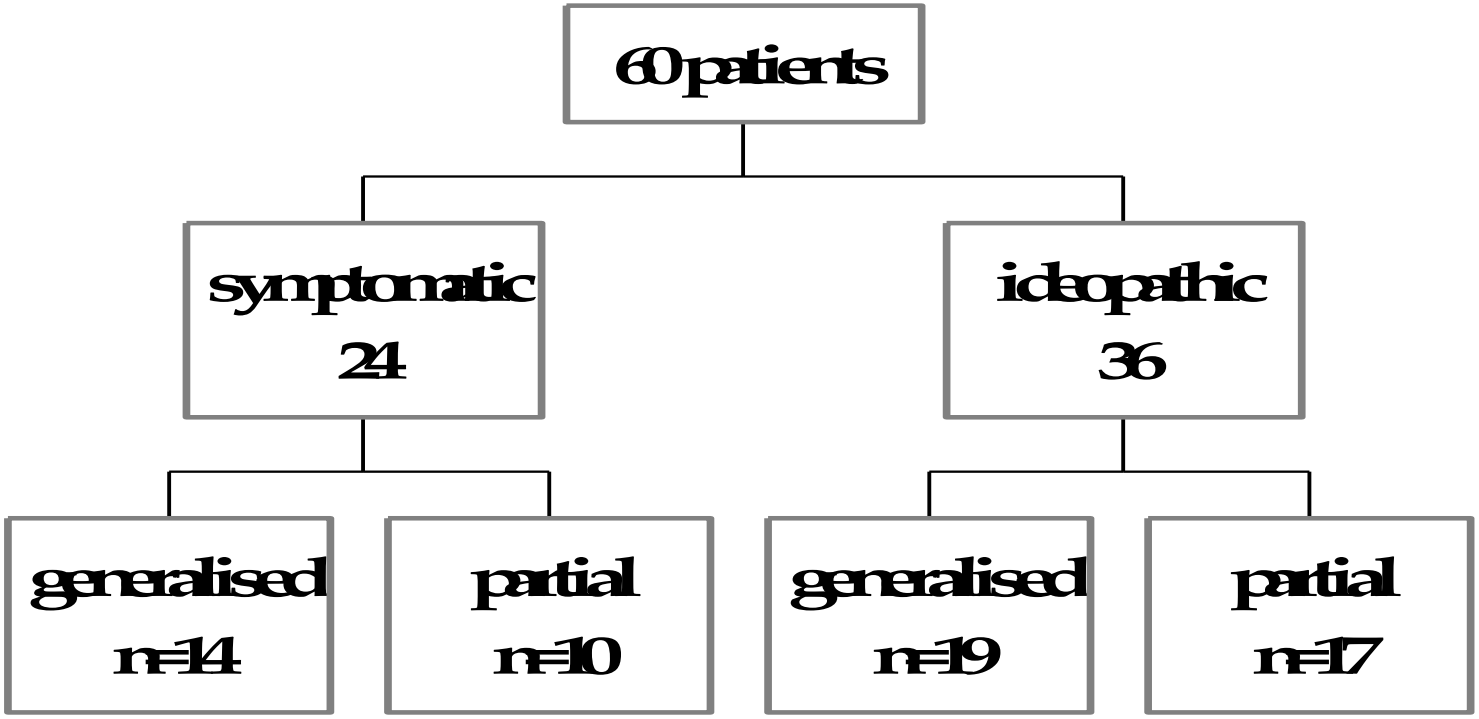
Seizure control

Treatment – antiepileptic drugs (AEDs)

Psychosocial environment

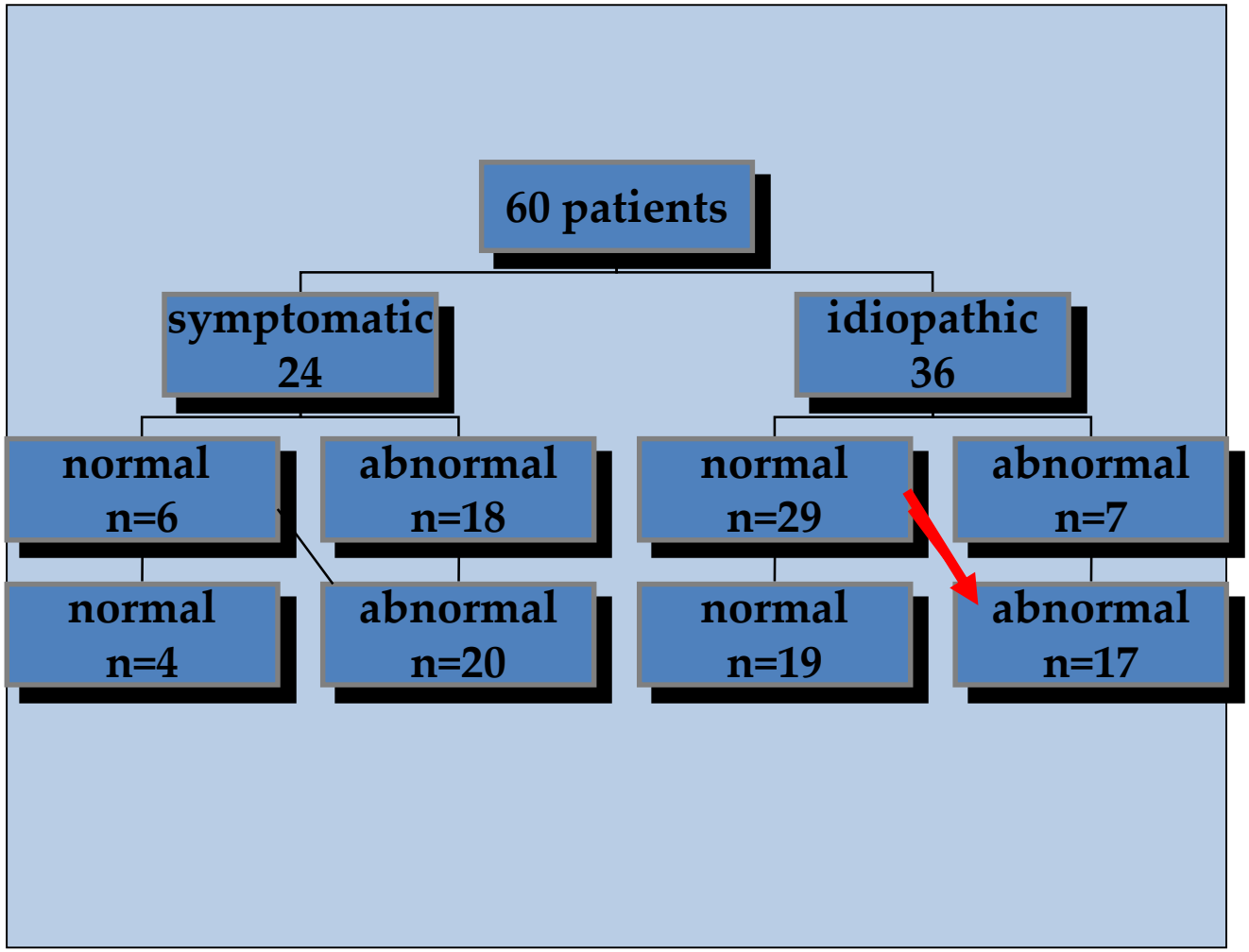
Seizure control

Prospective Study
Onset epilepsy < 1 year



Vanderlinden and Lagae, Pediatric Neurol, 2004, 31:52-55

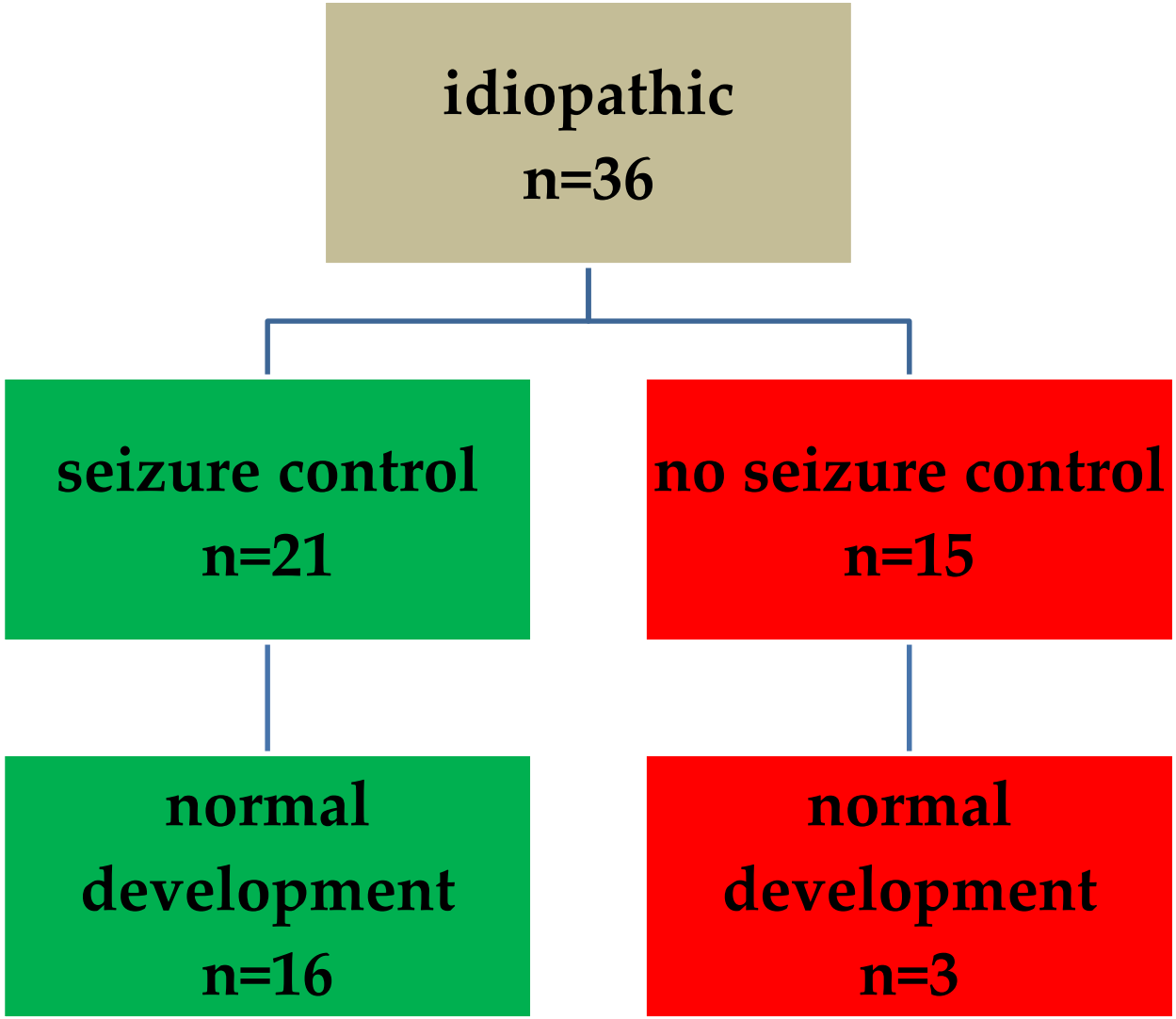
Early onset epilepsy : Cognitive Outcome



At onset

At end of follow-up

Cognitive outcome is related to seizure control



Global cognitive function in children with epilepsy: A community-based study

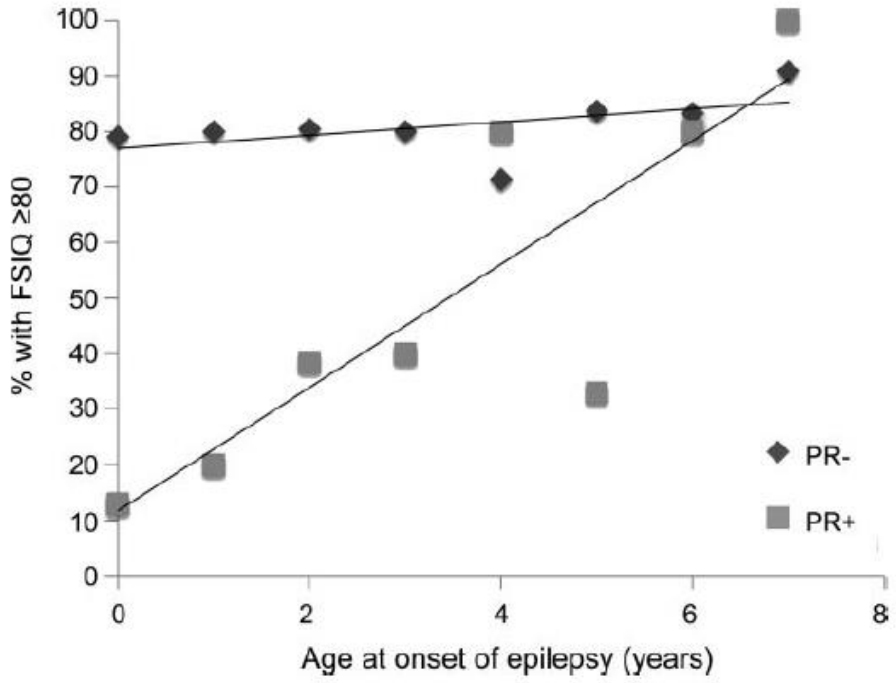
*Anne T. Berg, †John T. Langfitt, ‡§Francine M. Testa, ‡§Susan R. Levy, ¶Francis DiMario, #Michael Westerveld, and ¶Joseph Kulas

Negative predictive factors for cognitive outcome

Factor	Bivariate relative risk (95% CI) [p-value]
Age <5 years	2.89 (2.14, 3.90) [<0.0001]
Remote symptomatic etiology[a]	4.22 (3.30, 5.40) [<0.0001]
Epileptic encephalopathy	4.01 (3.26, 4.93) [<0.0001]
<5 years seizure-free	2.96 (2.16, 4.07) [<0.0001]
Current AED treatment	3.22 (2.40, 4.32) [<0.0001]

Epilepsia, 2008

Full scale IQ > 80 by age at onset and pharmaco-resistance



Cognitive dysfunctions in childhood epilepsy

Underlying etiology (structural, genetic,...)

Seizure type, **localization**

Seizure frequency, severity

Epilepsy syndrome

EEG abnormalities

Seizure control

Treatment – antiepileptic drugs (AEDs)

Psychosocial environment

Localization ?

Neuroscience Letters 507 (2012) 1–4

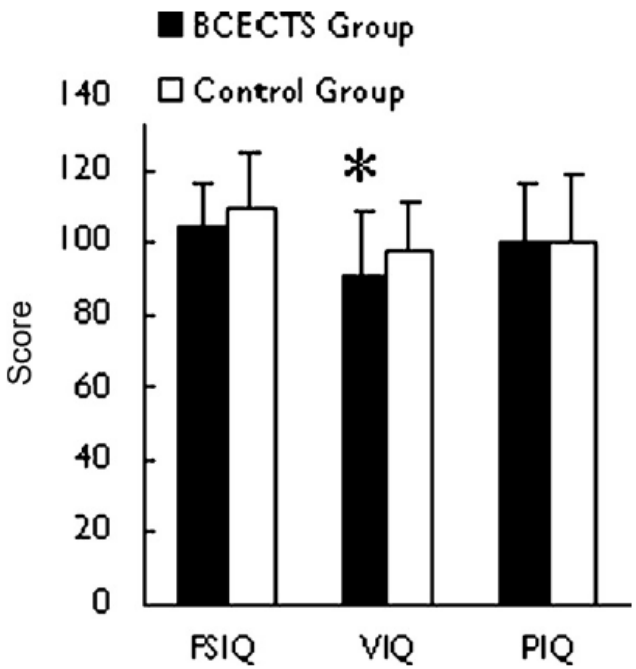
Contents lists available at SciVerse ScienceDirect

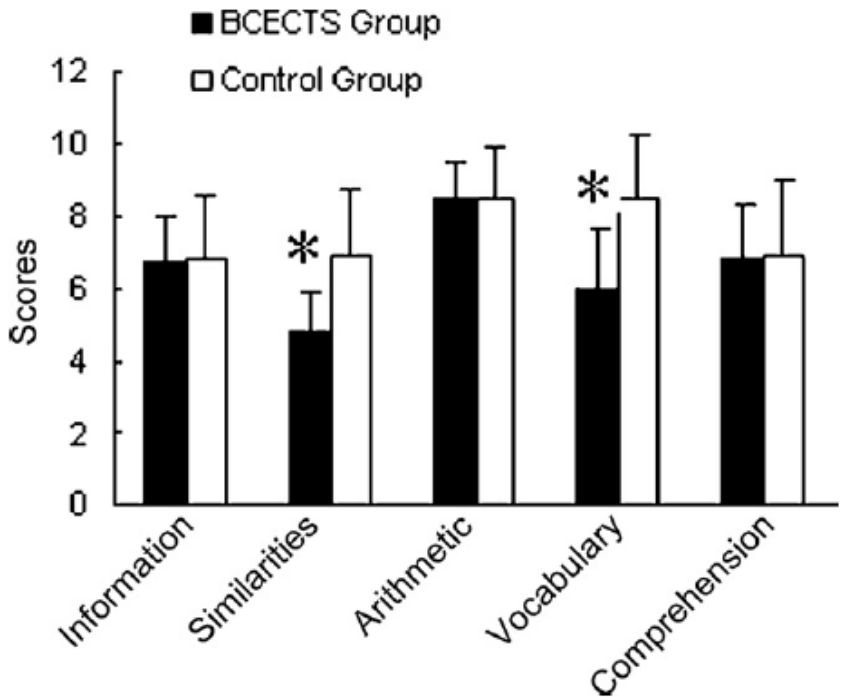
Neuroscience Letters

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

Cognition in Chinese children with benign childhood epilepsy with centrotemporal spikes (BCECTS)

Xinjie Liu[a], Xiaoli Zhang[b], Qizheng Han[c], Jing Guo[a], Chunting Wang[d,*]





Effect on school performance

Table II: Intellectual level, memory, and visuospatial abilities in the rolandic epilepsy (RE) and control groups

	RE Mean (SD)	*Controls Mean (SD)*	*t-test (p)*
WISC-R[20]	108.7 (11.2)	110.4 (13.2)	ns
TEMA word repetition[22]	112.4 (42.6)	120.5 (45.2)	ns
TEMA digit backward[22]	97.9 (30.4)	109.1 (38.9)	ns
TEMA digit forward[22]	93.1 (33.8)	108.9 (33.2)	ns
Visual motor integration[23]	102.7 (23.3)	118.4 (20.8)	0.03

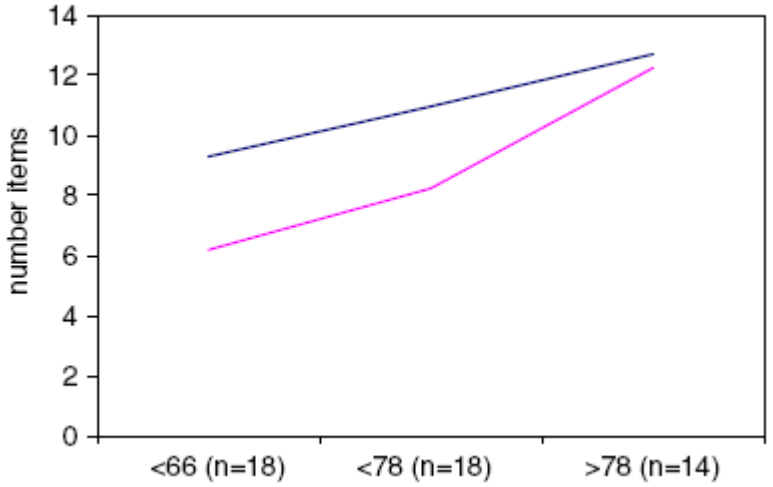
WISC-R, Wechsler Intelligence Scale for Children-Revised; TEMA, Test for Memory and Learning; ns, not significant.

Table III: Distribution of specific learning disabilities and attention deficits in the rolandic epilepsy (RE) and control groups

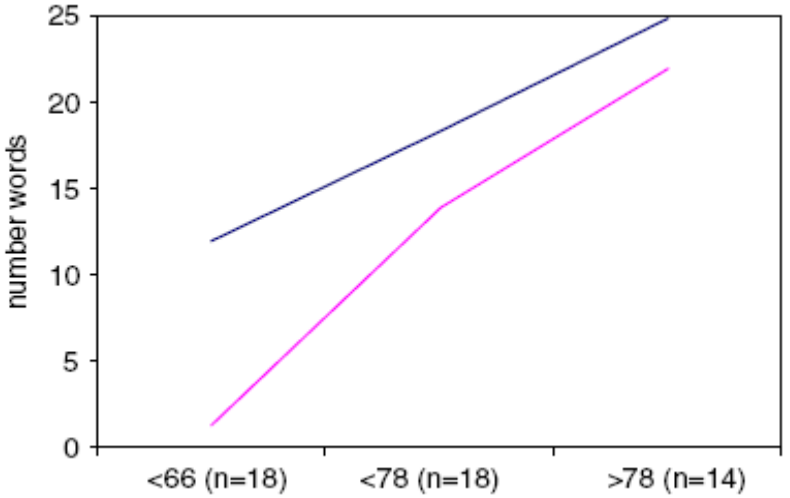
	RE n (%)	*Controls n (%)*	*χ2*
Dyslexia-dysgraphia[27,28]	9/20 (45.0)	2/21 (9.5)	0.01
Dyscalculia[29]	5/16 (31.3)	1/17 (5.9)	0.06
Attention deficits[21]	11/20 (55.0)	6/21 (28.6)	0.09

Developmental Medicine & Child Neurology 2008, 50: 353–356

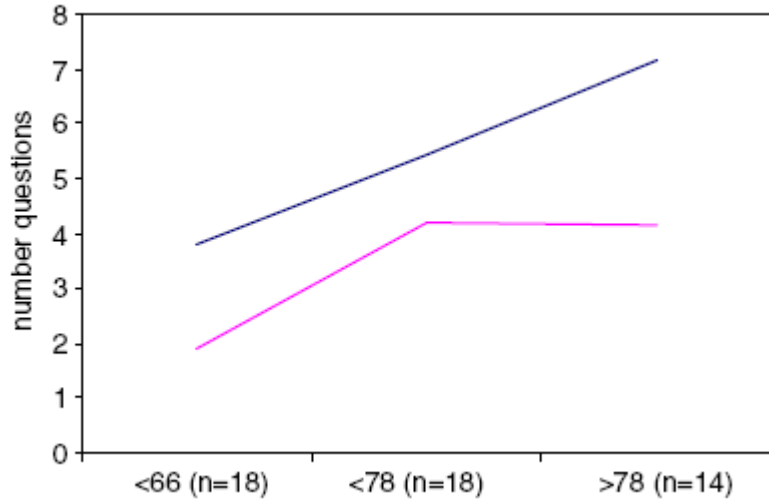
Age dependency of cognitive problems



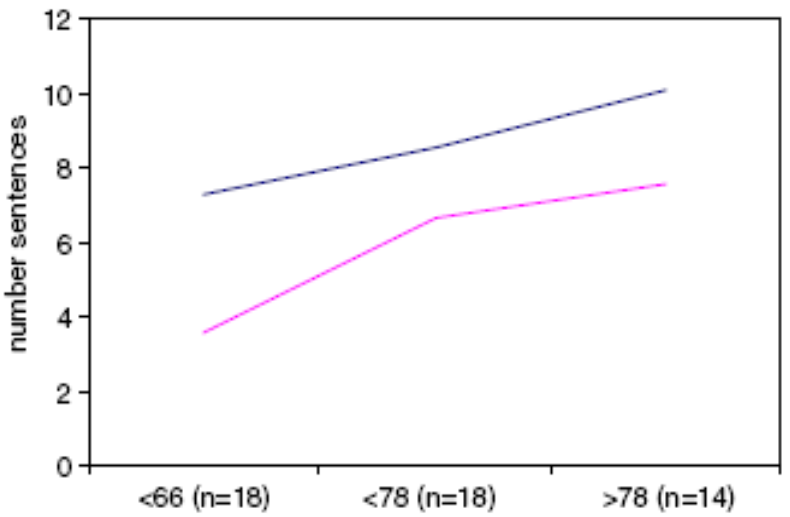
Spatial perception



Word fluency



Language comprehension



Auditory memory

Danielsson and Petermann, Epilepsy & Behavior 2009, 16:646-651

Serial changes of prefrontal lobe growth in the patients with benign childhood epilepsy with centrotemporal spikes presenting with cognitive impairments/behavioral problems

Hideaki Kanemura [a,*], Sonoko Hata [a], Kakuro Aoyagi [a], Kanji Sugita [a], Masao Aihara [b]

[a] *Department of Pediatrics, Faculty of Medicine, University of Yamanashi, 1110 Chuo, Yamanashi 409-3898, Japan*
[b] *Department of Health Science and Community, Faculty of Medicine, University of Yamanashi, 1110 Chuo, Yamanashi 409-3898, Japan*

Received 30 November 2009; received in revised form 2 March 2010; accepted 11 March 2010

Brain and Development 2011

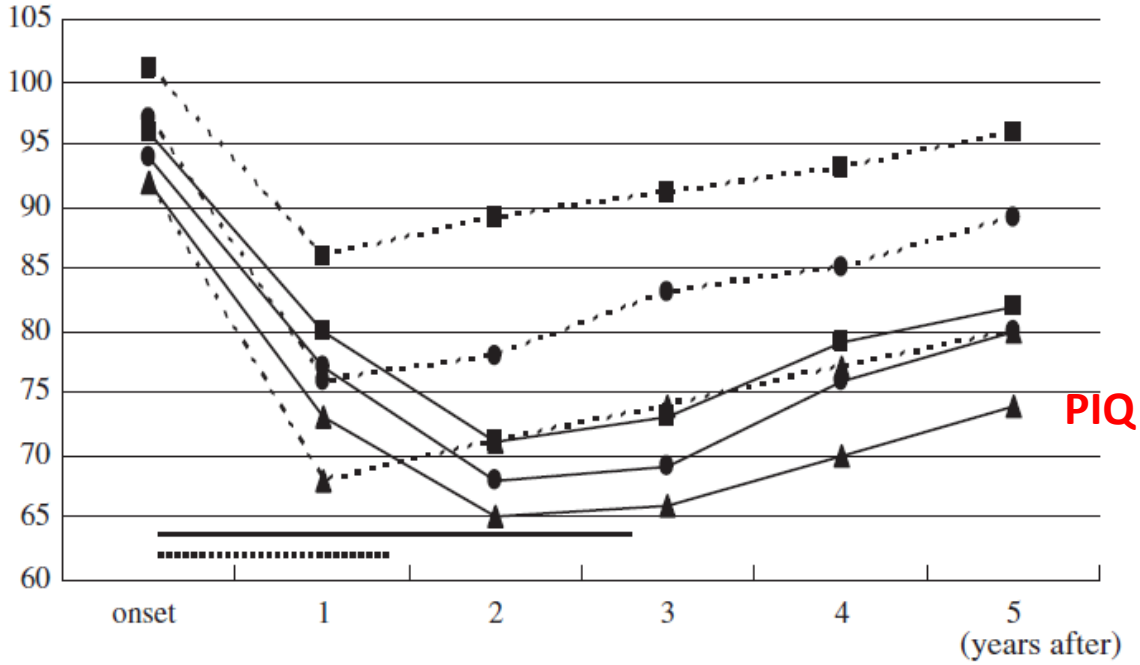
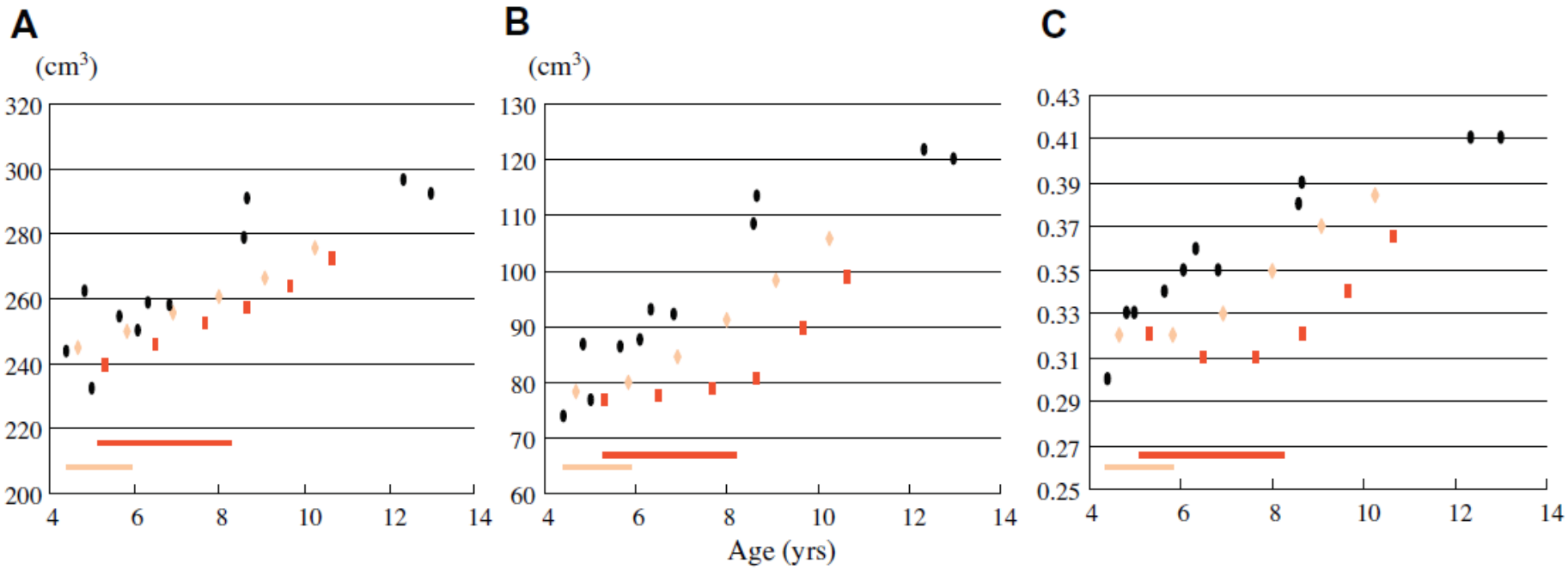


Fig. 1. Serial changes of FIQ, VIQ and PIQ on WISC-III with the exception of the onset of Case 2 in the two patients with BCECTS(+) (Case 1, solid lines; Case 2, dotted lines). Each symbol for circles, squares, and triangles indicates FIQ, VIQ, and PIQ, respectively. Scores of the onset in Case 2 showed the score on WPPSI. Horizontal bars for Case 1 (solid line) and Case 2 (dotted line) indicate active seizure period.

Serial changes of frontal lobe volumes



Epilepsia, 52(5):849–856, 2011
doi: 10.1111/j.1528-1167.2011.03057.x

CRITICAL REVIEW AND INVITED COMMENTARY

Cognitive and behavioral complications of frontal lobe epilepsy in children: A review of the literature

*†‡Hilde M. H. Braakman, †‡§Maarten J. Vaessen, †‡§Paul A. M. Hofman, †Mariette H. J. A. Debeij-van Hall, ‡§Walter H. Backes, *†‡Johan S. H. Vles, and *†‡Albert P. Aldenkamp

*Department of Neurology, Maastricht University Medical Centre, Maastricht, The Netherlands; †Department of Research and Development, Epilepsy Centre Kempenhaeghe, Heeze, The Netherlands; §Department of Radiology, Maastricht University Medical Centre, Maastricht, The Netherlands; and ‡Research School for Mental Health and Neuroscience, Maastricht University Medical Centre, Maastricht, The Netherlands

Table 1. Etiology of frontal lobe epilepsy in children

References	Number of patients	Etiology on basis of MRI
Auclair et al. (2005)	8	3/8 symptomatic 5/8 cryptogenic
Aoyagi et al. (2005)	12	5/12 symptomatic 7/12 cryptogenic
Jocić-Jakubi et al. (2009)	10	10/10 cryptogenic
Lagae et al. (2001)	7	7/7 cryptogenic
Lawson et al. (2002)	38	12/38 symptomatic 26/38 cryptogenic
Nolan et al. (2004)	25	7/25 symptomatic 18/25 cryptogenic
Sinclair et al. (2004)	22	4/22 symptomatic 18/22 cryptogenic
Total	122	31/122 (25%) symptomatic 91/122 (75%) cryptogenic

Wide range of cognitive impairments

Table 2. A summary of the main studies of children with FLE who had undergone neuropsychological assessment and their findings

References	Number of patients	Neuropsychological impairments
Auclair et al. (2005)	8	Attention deficits
Culhane-Shelburne et al. (2002)	12	Deficits in executive functions
Hernandez et al. (2003)	16	Deficits in executive functions, attention, and behavior
Lassonde et al. (2000)	16	Deficits in executive functions, attention, behavior, and motor skills
Lendt et al. (2002)	12	Deficits in motor coordination, short- and long-term memory, attention, and executive functions
Nolan et al. (2004)	25	Memory impairment
Prévost et al. (2006)	21	Deficits in attention, behavior, language, memory, and cognition
Riva et al. (2002)	8	Deficits in attention, behavior, and executive functions
Riva et al. (2005)	17	Deficits in executive functions
Sinclair et al. (2004)	14	Below normative IQ scores, impaired fine-motor coordination, deficits in attention, behavior and executive functions

Epilepsia, 52(9):1685–1691, 2011
doi: 10.1111/j.1528-1167.2011.03085.x

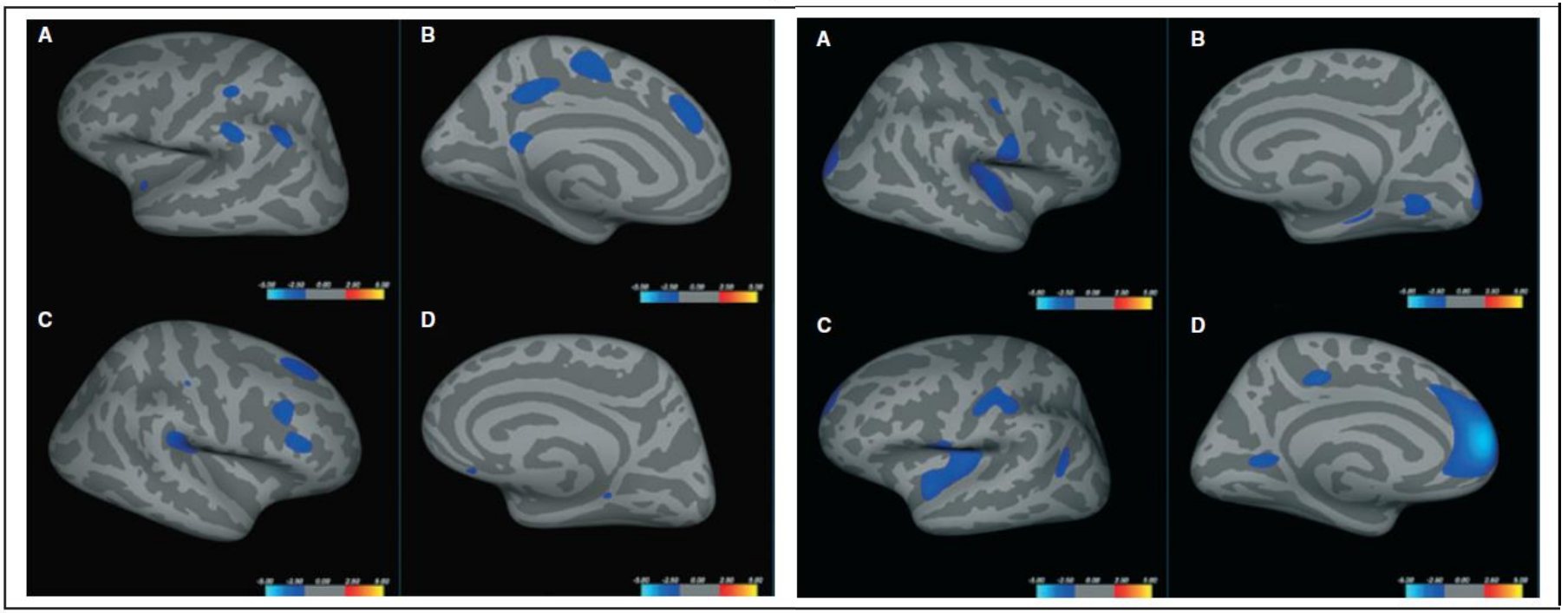
FULL-LENGTH ORIGINAL RESEARCH

Widespread cortical thinning in children with frontal lobe epilepsy

*†Elysa Widjaja, *Sina Zarei Mahmoodabadi, †O. Carter Snead III, *Abeer Almehdar, and ‡Mary Lou Smith

*Diagnostic Imaging, Hospital for Sick Children, Toronto, Ontario, Canada; †Division of Neurology, Hospital for Sick Children, Toronto, Ontario, Canada; and ‡Department of Psychology, Hospital for Sick Children, Toronto, Ontario, Canada

Refractory frontal lobe epilepsy



Left frontal epilepsy

Right frontal epilepsy

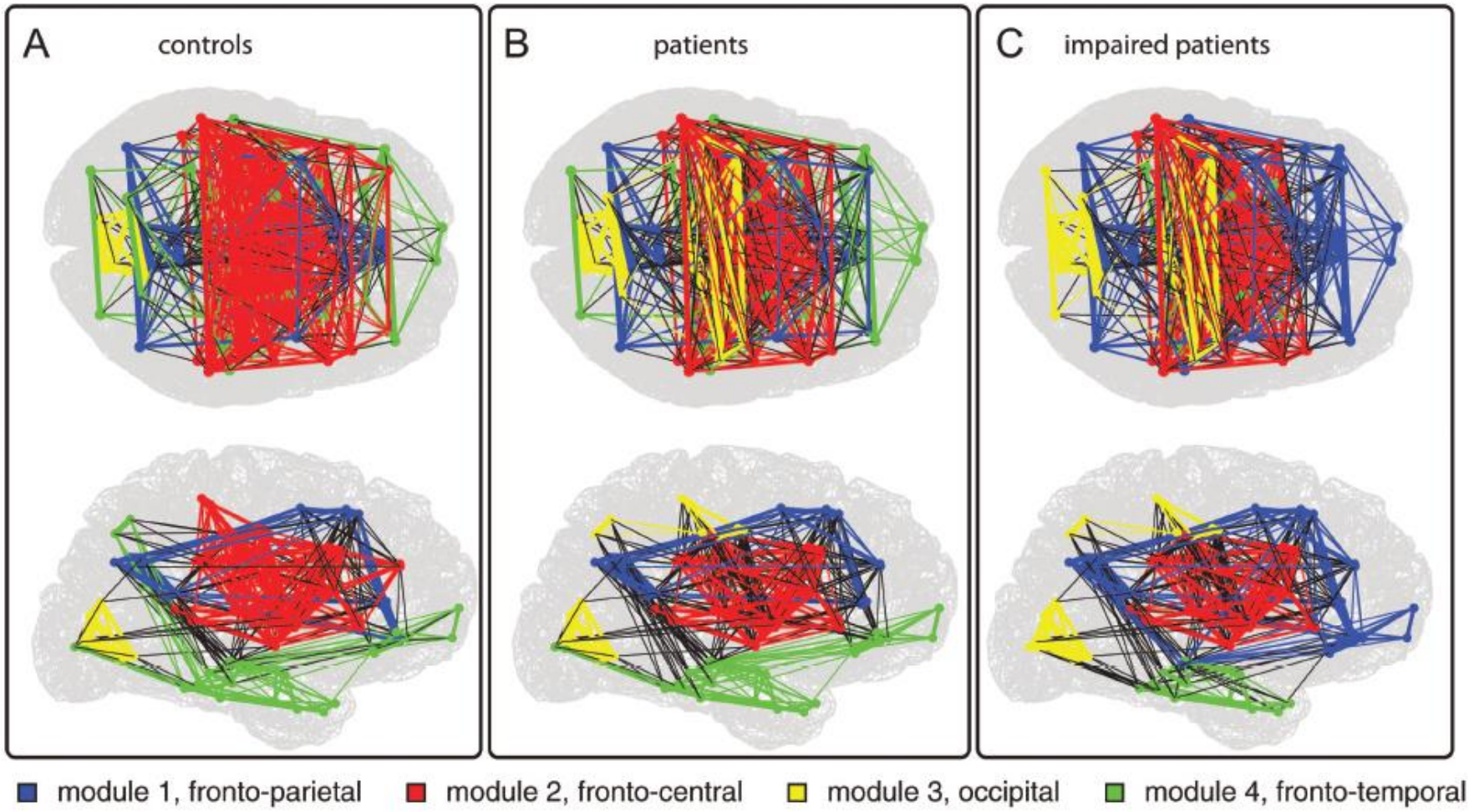
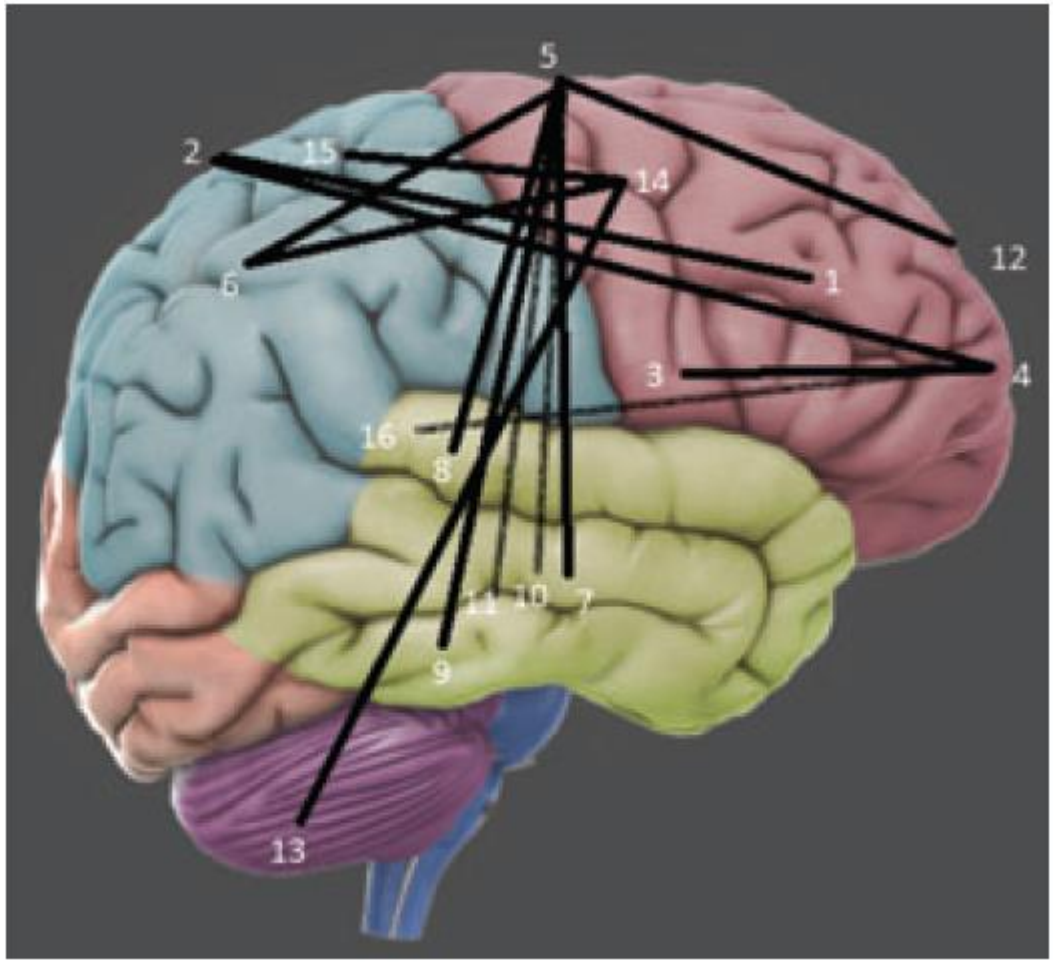


Figure 4. In the OCS, four distinct modules of the cerebrum are visualized by different colors (as in Fig. 1) for the healthy controls (*A*), the full patient group (*B*), and the cognitively impaired patient subgroup. Module 1 (blue) extends from fronto-parietal regions in controls to more prefrontal and latero-frontal regions in patients, particularly for the cognitively impaired patients. Module 2 (red) reveals no apparent differences between patients and controls. Module 3 (yellow) extends from mere posterior occipital regions in controls to parietal and more latero-occipetal regions in patients. Module 4 (green) curtails from occipital, parietal, temporal, and frontal regions to temporal and frontal regions.

Concept of **diseased networks**



Explains variety
of cognitive problems

Secondary?

Reversible?

Cognitive dysfunctions in childhood epilepsy

Underlying etiology (structural, genetic,...)

Seizure type, localization

Seizure frequency, severity

Epilepsy syndrome

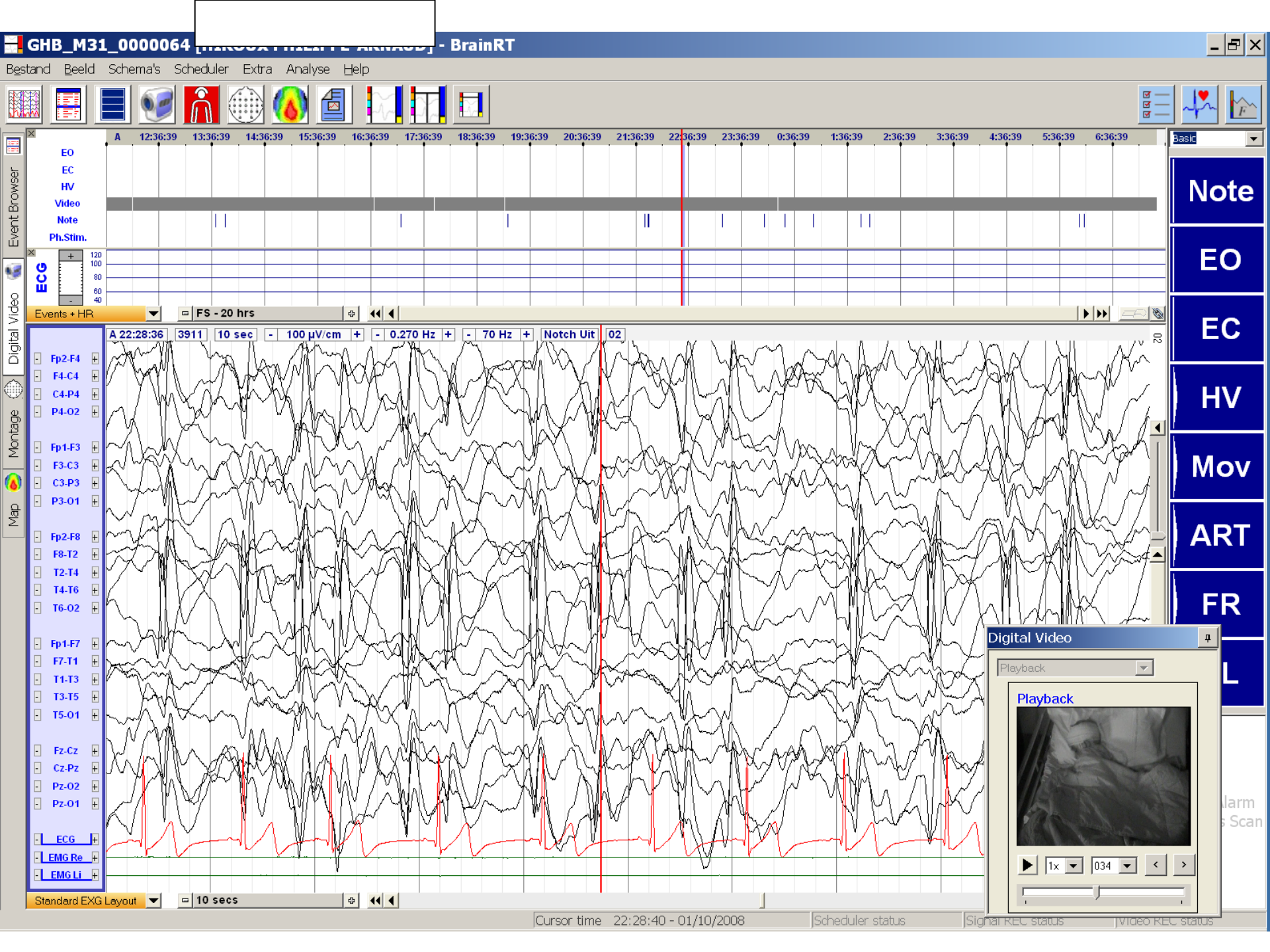
EEG abnormalities

Seizure control

Treatment – antiepileptic drugs (AEDs)

Psychosocial environment

EEG ?


GHB_M31_0000064 - BrainRT
Bestand Beeld Schema's Scheduler Extra Analyse Help
EO
EC
HV
Video
Note
Ph.Stim.
ECG
Events + HR
FS - 20 hrs
A 22:28:36
3911
10 sec
100 µV/cm
0.270 Hz
70 Hz
Notch Uit
02
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F8
F8-T2
T2-T4
T4-T6
T6-O2
Fp1-F7
F7-T1
T1-T3
T3-T5
T5-O1
Fz-Cz
Cz-Pz
Pz-O2
Pz-O1
ECG
EMG Re
EMG Li
Standard EXG Layout
10 secs
Basic
Note
EO
EC
HV
Mov
ART
FR
Digital Video
Playback
Playback
Cursor time 22:28:40 - 01/10/2008
Scheduler status
Signal REC status
Video REC status
Event Browser
Digital Video
Montage
Map

EEG and cognition

EEG patterns with

known negative cognitive outcome

- hypsarrhythmia
- suppression burst patterns
- slow spike waves
- **CSWSS**

→ All spikes negative influence on cognition ?

EEG abnormalities and cognition

Transient Cognitive Impairment (TCI)

acute cognitive dysfunction

(processing speed, working memory, focused attention)

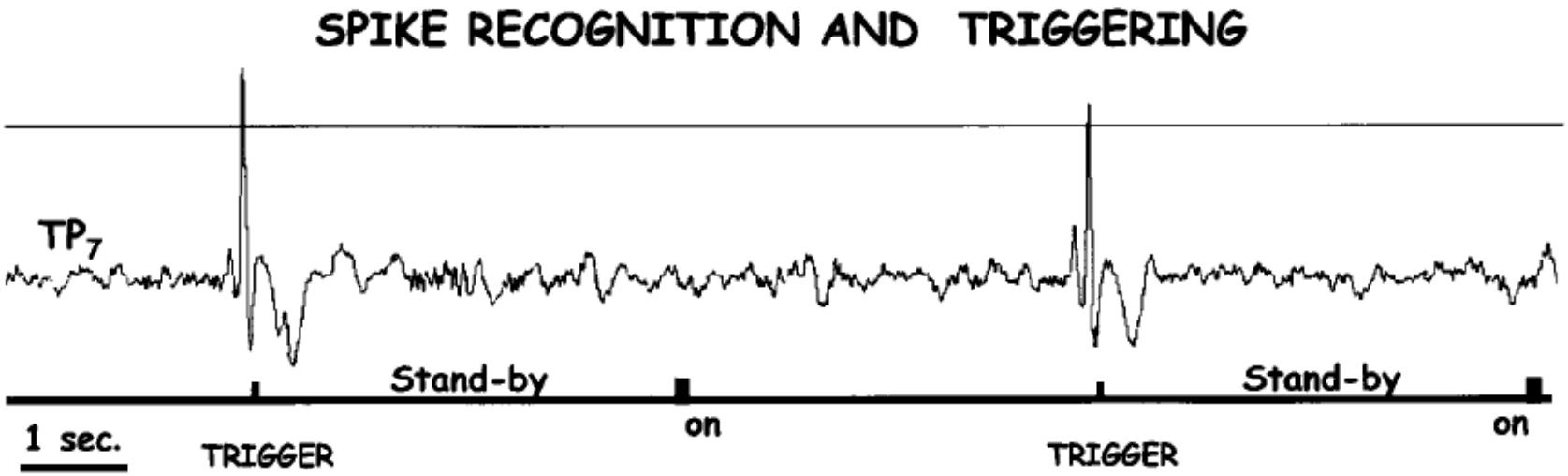
around the time of epileptic discharges

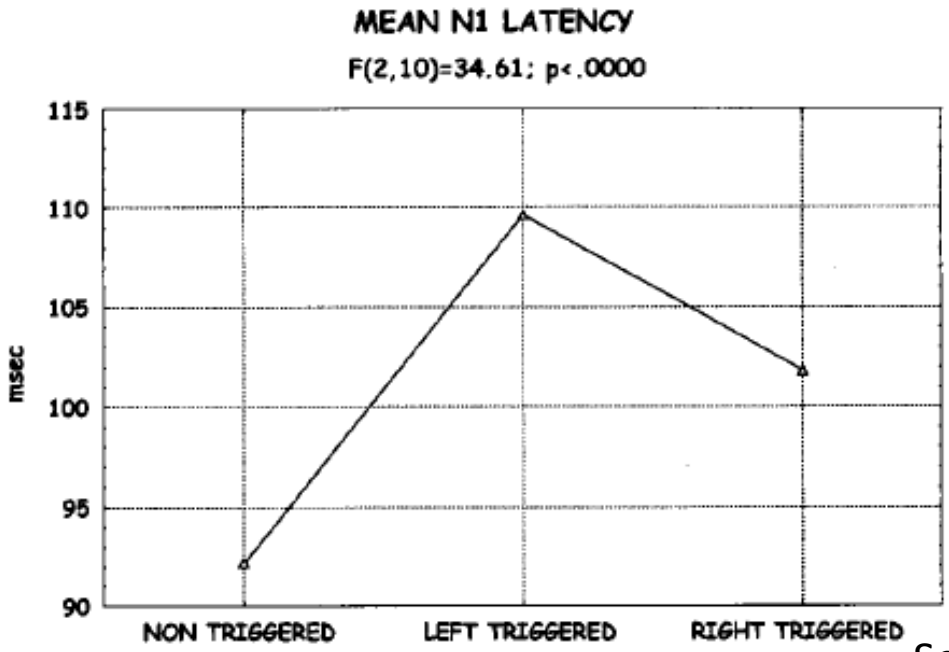
(absences,…)

Cumulative effects of spikes on cognition independent of underlying pathology

(Rolandic Epilepsy, CSWSS, epileptic encephalopathies)

Spike triggered auditory evoked potentials in Landau Kleffner syndrome



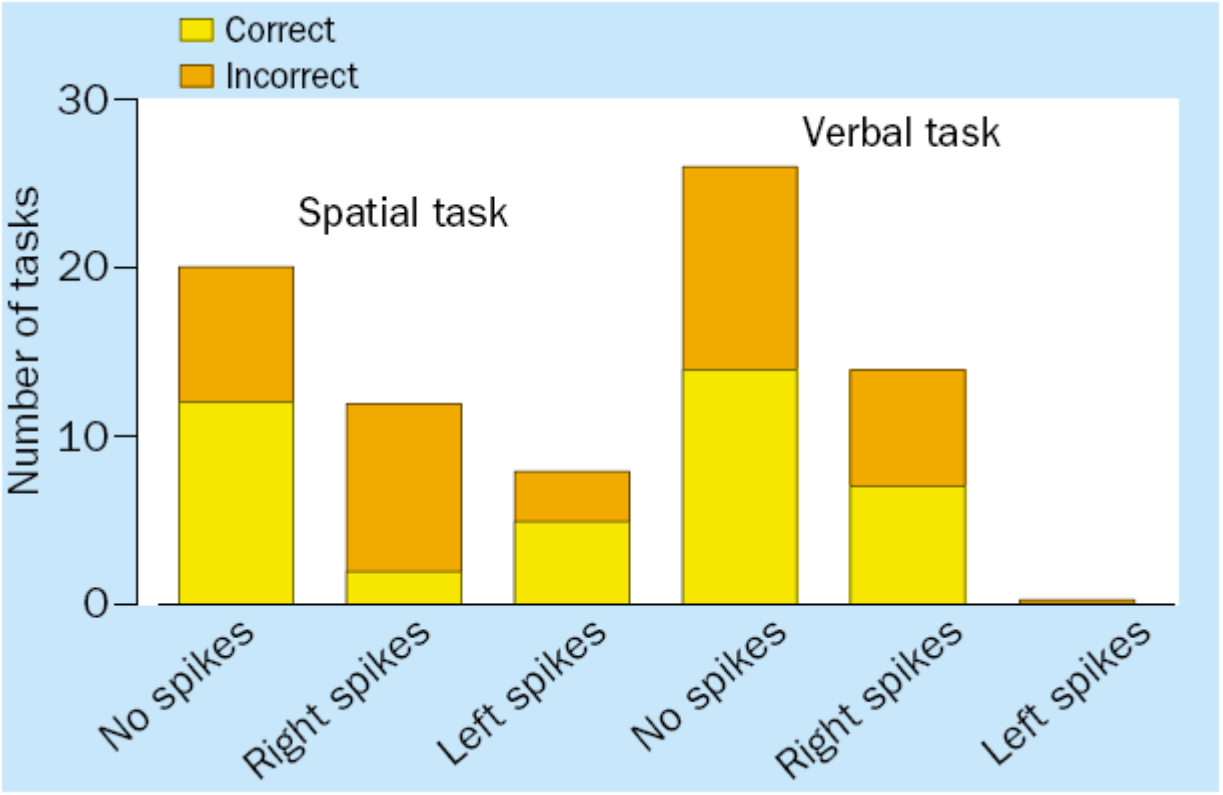


1 single spike changes auditory processing

Seri et al, 1998

Cognitive impairment during epileptiform discharges: is it ever justifiable to treat the EEG?

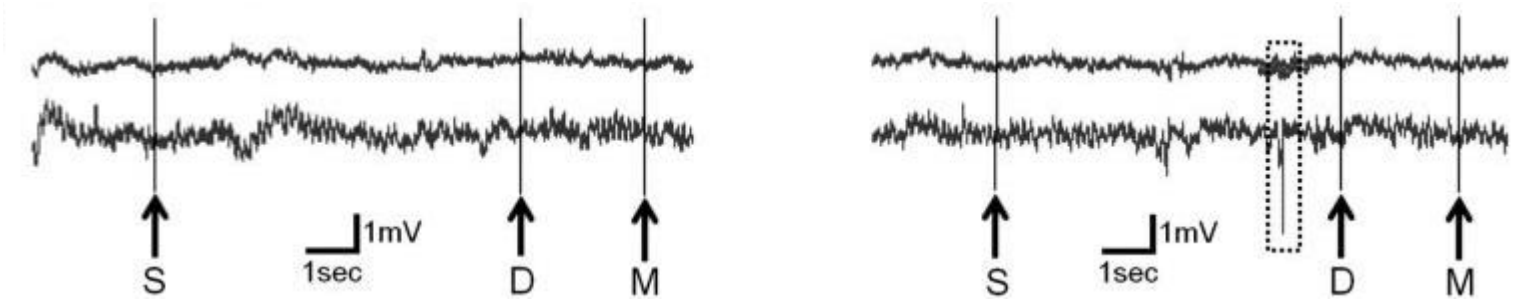
Colin D Binnie



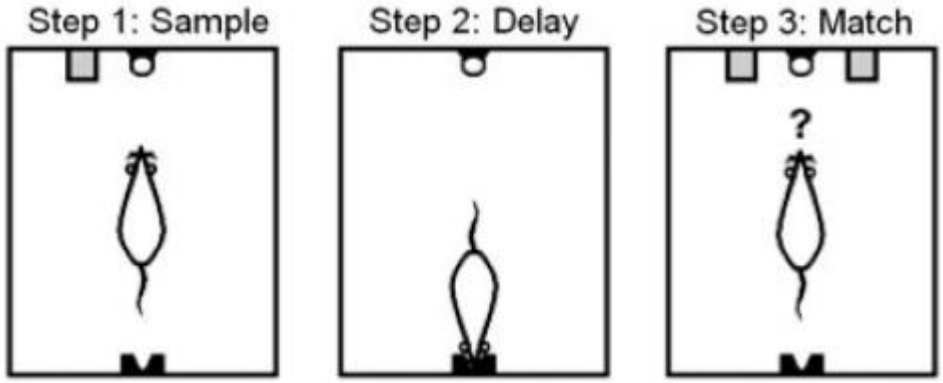
Lancet Neurol 2003; **2:** 725–30

Hippocampal interictal spikes disrupt cognition in rats

Kleen JK, Scott R, Holmes GL, Lenck-Santini PP, Ann Neurol 2010

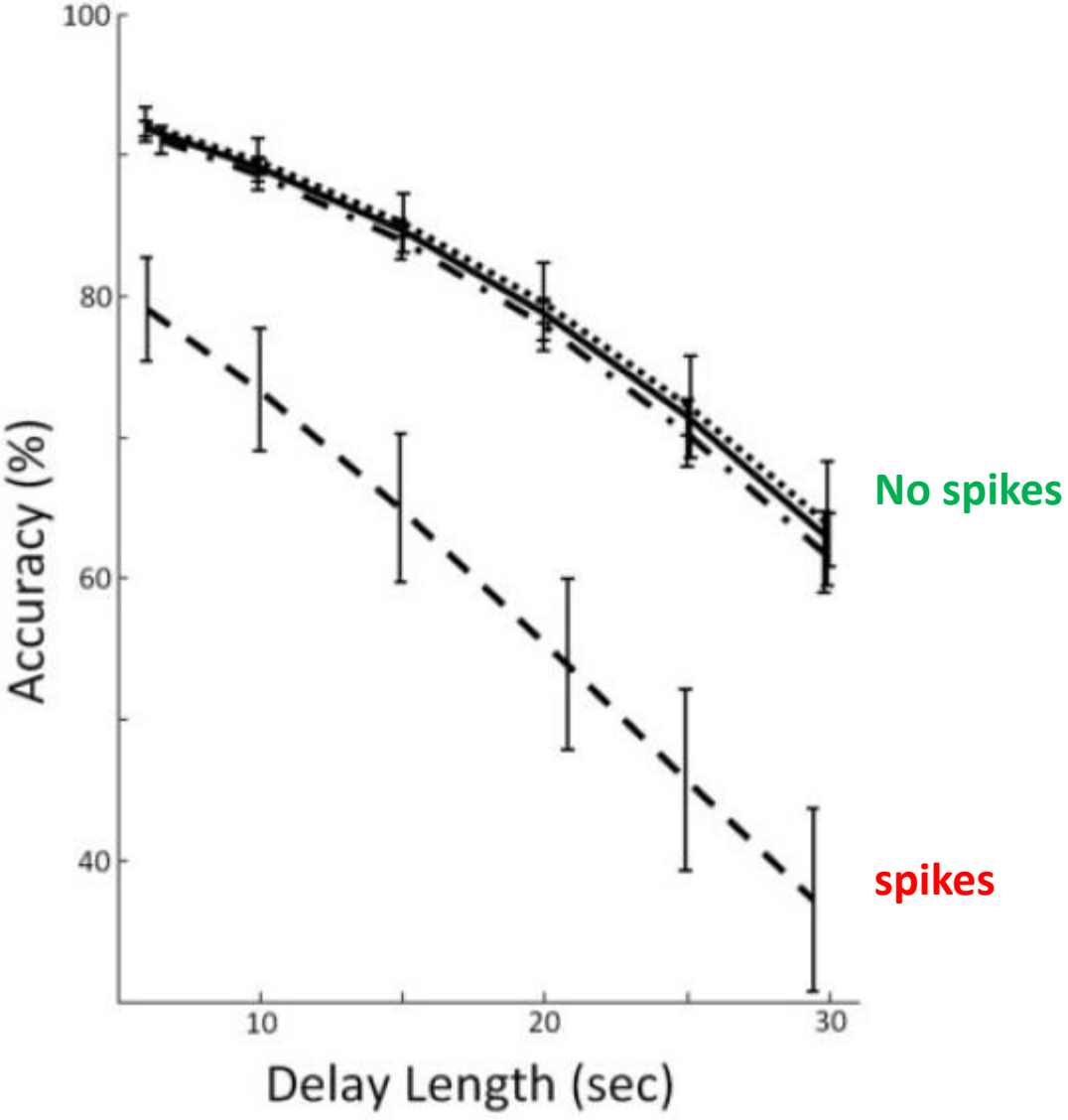


Delayed match to sample



encoding maintenance retrieval

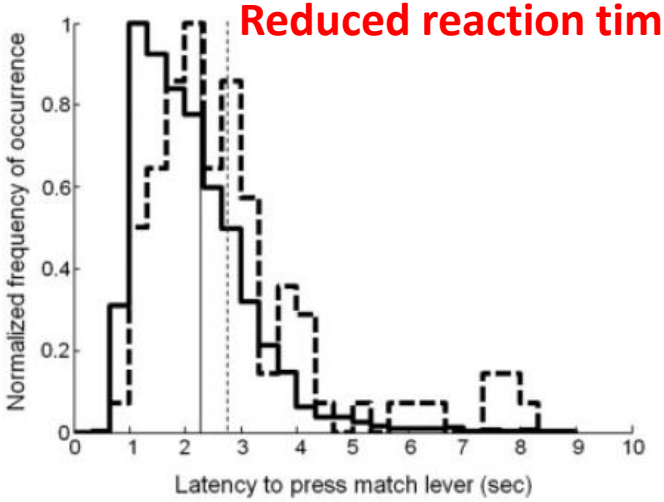
Specific memory impairment



No spikes

spikes

Reduced reaction times



Cumulative effects of spikes : CSWSS as a model

Epilepsy & Behavior 22 (2011) 518–522

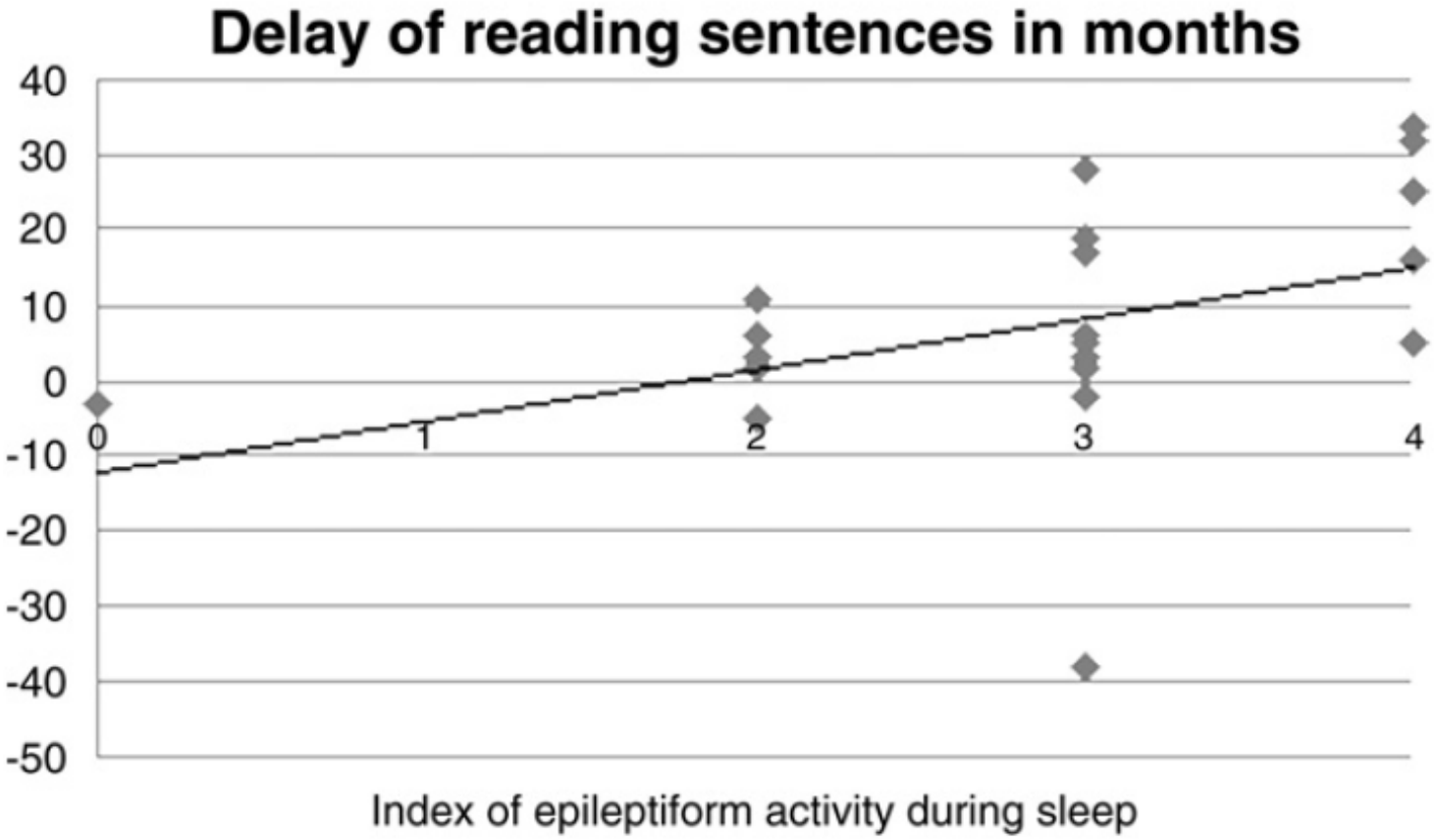
Contents lists available at SciVerse ScienceDirect

Epilepsy & Behavior

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

Reading performance in children with rolandic epilepsy correlates with nocturnal epileptiform activity, but not with epileptiform activity while awake

S.C.M. Ebus [a,*], G.M. Overvliet [a,b,c], J.B.A.M. Arends [a], A.P. Aldenkamp [a,b,c]



Effect of CSWSS on cognitive consolidation during the night

Clinical Neurophysiology 122 (2011) 1779–1787

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

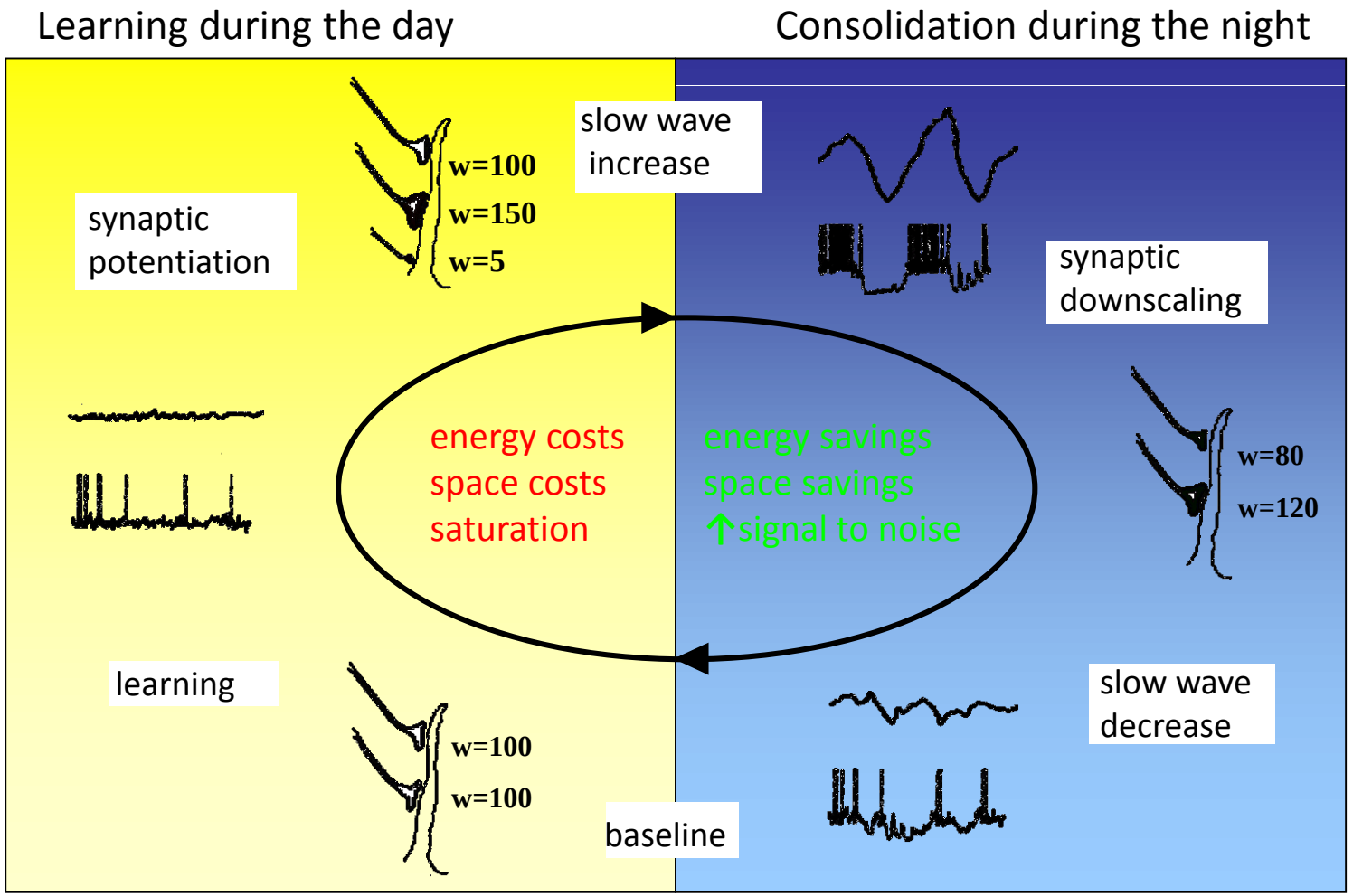
Impaired slow wave sleep downscaling in encephalopathy with status epilepticus during sleep (ESES)

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

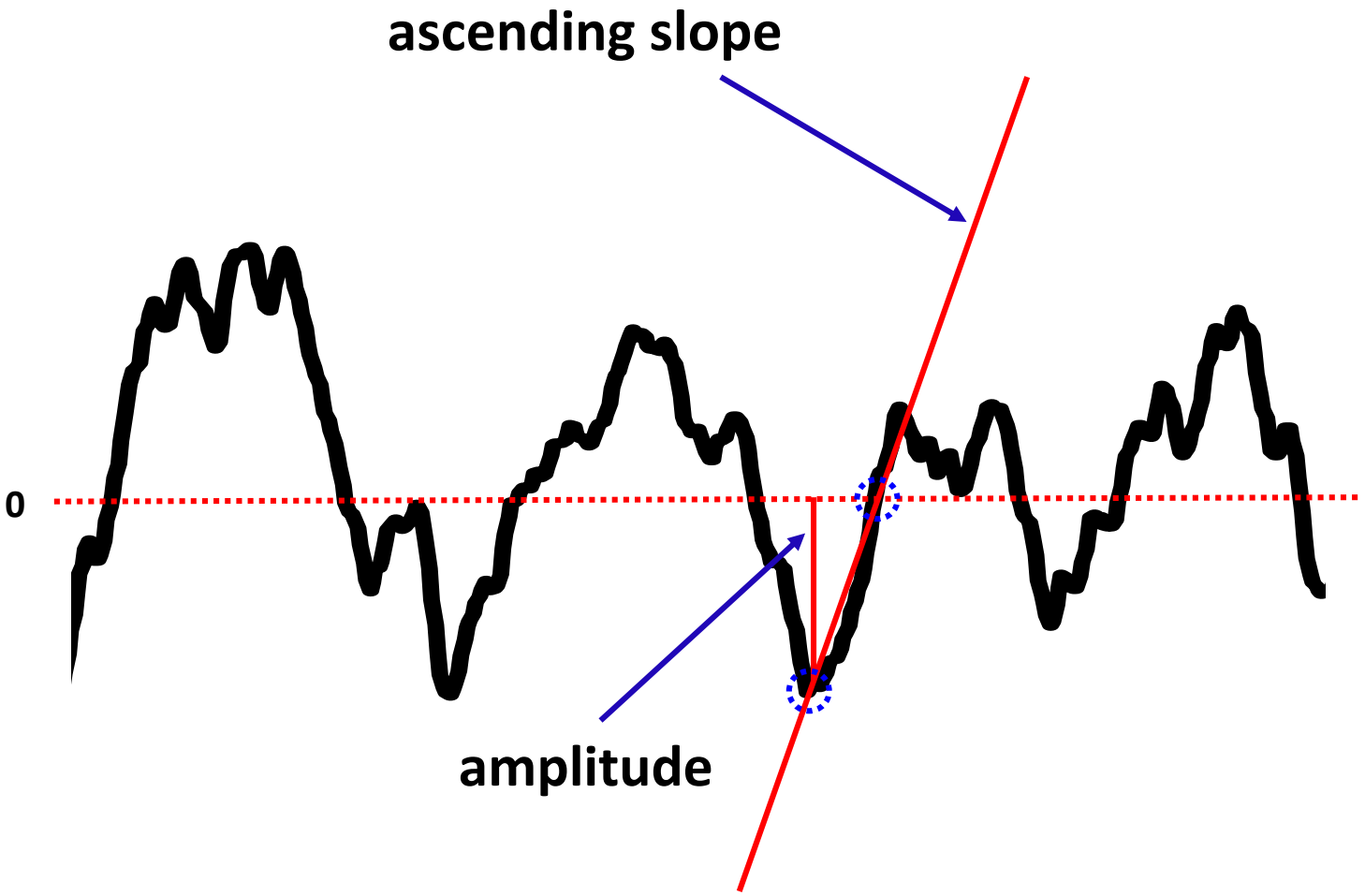
[a] Division of Clinical Neurophysiology, University Children's Hospital Zurich, Zurich, Switzerland
[b] Department of Paediatric Neurology, University Children's Hospital, Heidelberg, Germany
[c] Epilepsy Centre Kork, Kehl-Kork, Germany
[d] Bernstein Center for Computational Neuroscience, Charité – University Medicine Berlin, Germany
[e] Child Development Centre, University Children's Hospital Zurich, Zurich, Switzerland

- Encephalopathy with status epilepticus during sleep (ESES) is associated with cognitive regressions.
- The overnight decrease of EEG slow wave slopes was linked to slow wave sleep downscaling.
- This downscaling process is thought to be a plasticity process important for learning and memory.
- Children with ESES do not show such a decrease in slope during overnight sleep.
- This lack of downscaling in ESES children may be responsible for the cognitive regressions.

Physiological sleep: Synaptic homeostasis hypothesis

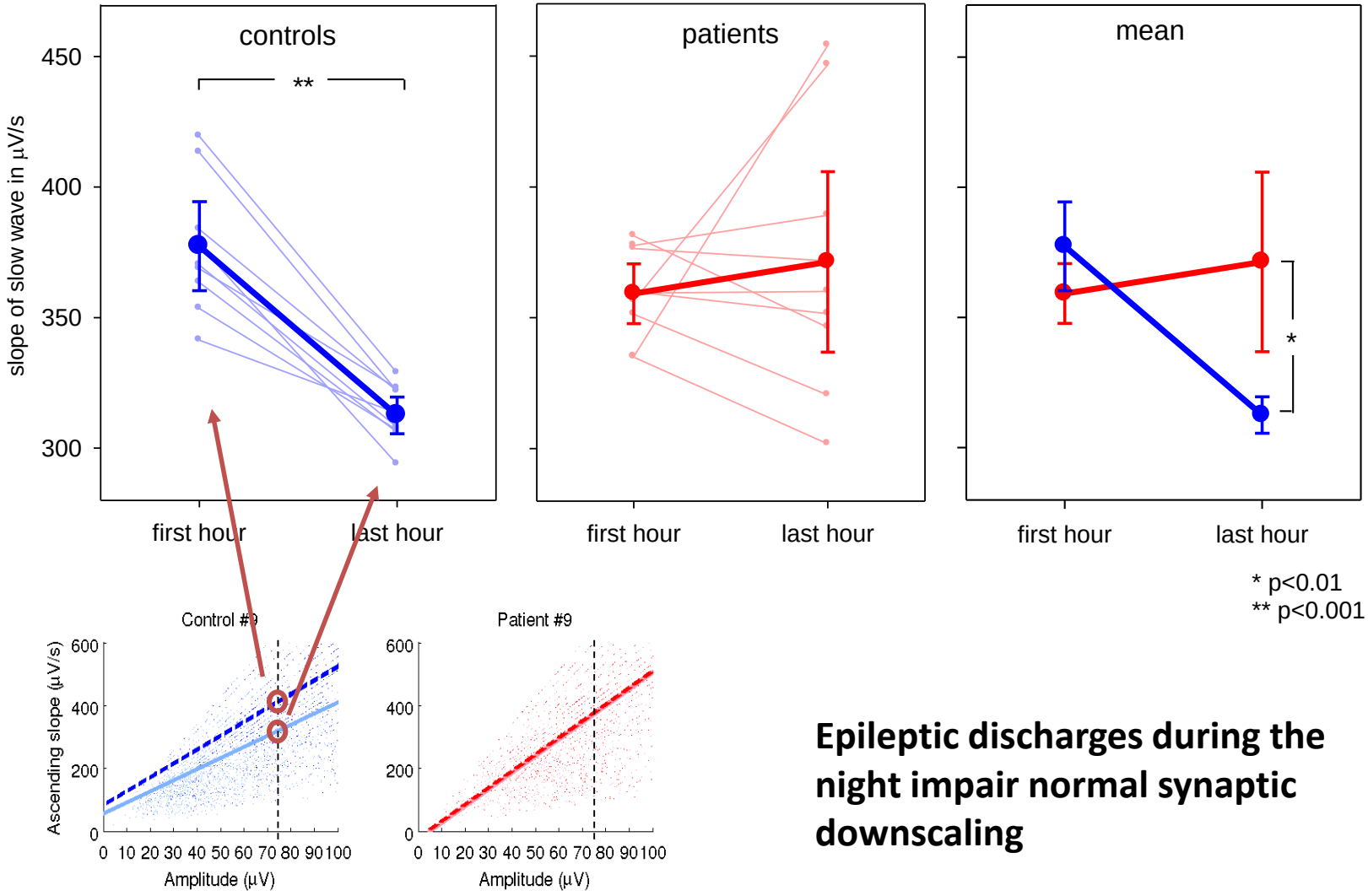


Tononi and Cirelli, 2006



Kurth et al. 2010

Normal situation :
Slope of slow waves decreases during the night: synaptic downscaling



Epileptic discharges during the night impair normal synaptic downscaling

Cognitive dysfunctions in childhood epilepsy

Underlying etiology (structural, genetic,...)

Seizure type, localization

Seizure frequency, severity

Epilepsy syndrome

EEG abnormalities

Seizure control

Treatment – antiepileptic drugs (AEDs)

Psychosocial environment

Epilepsy syndrome ?

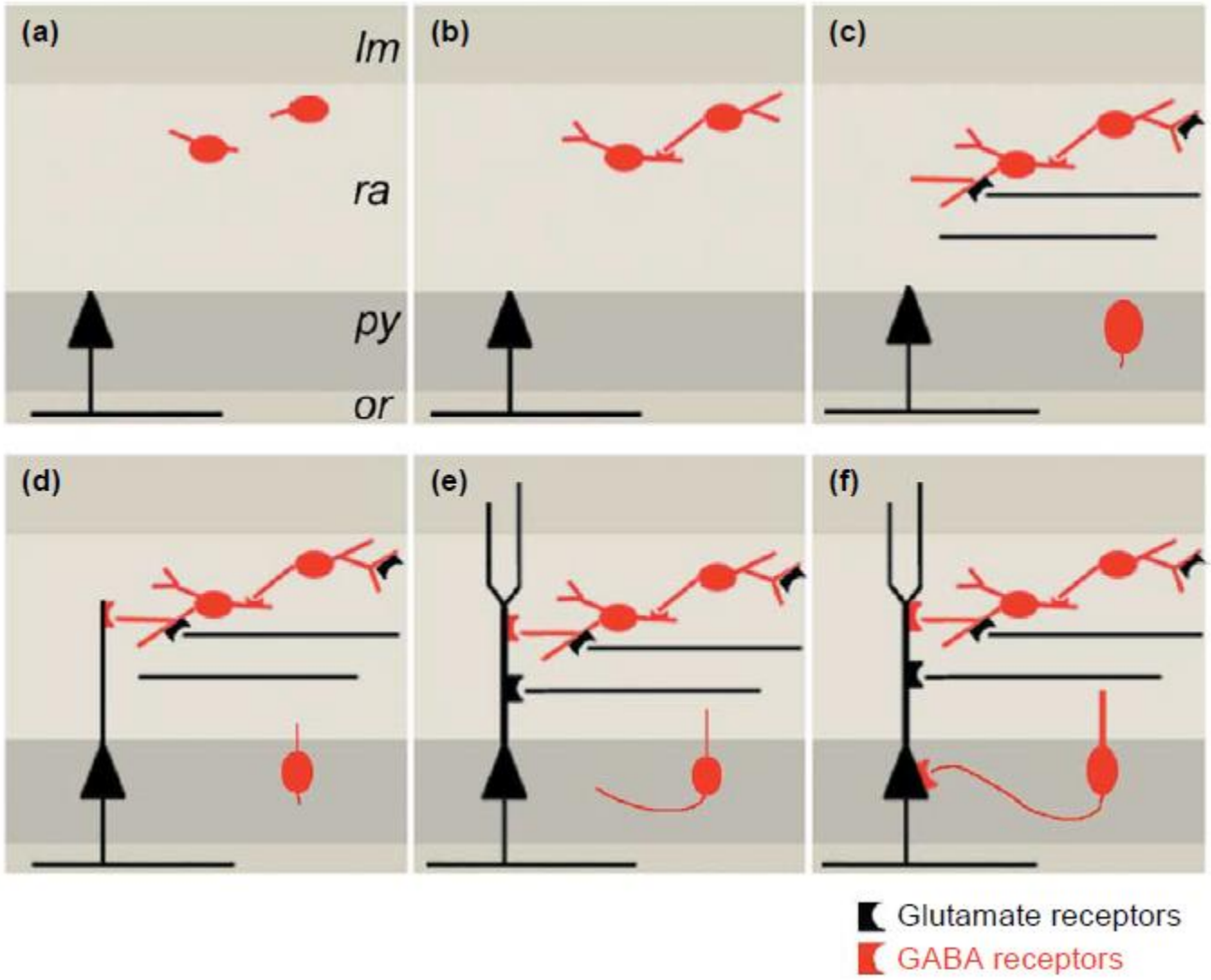
Epileptic encephalopathies: Dravet syndrome
How to explain cognitive decline?

- Number of seizures ?
- Status epilepticus ?
- Early epilepsy onset ?
- EEG ?

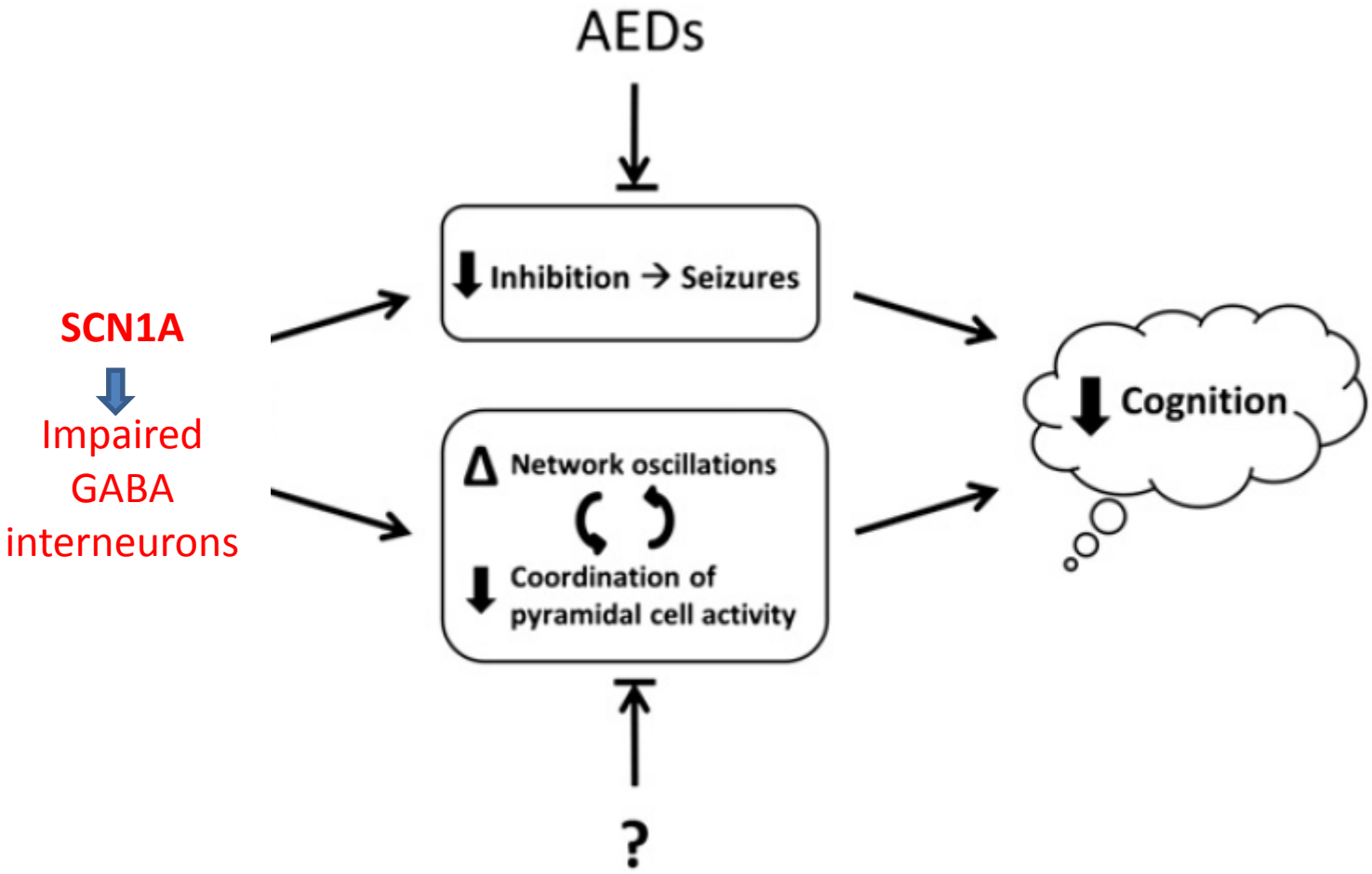
Or

- SCN1A is a **developmental gene** ?

Mutations in SCN1A impair GABA interneurons (animal models)



Bender et al, Epilepsy and Behavior, 2012



Bender et al , Epilepsy and Behaviour, 2012

Cognitive dysfunctions in childhood epilepsy

Underlying etiology (structural, genetic,...)

Seizure type, localization

Seizure frequency, severity

Epilepsy syndrome

EEG abnormalities

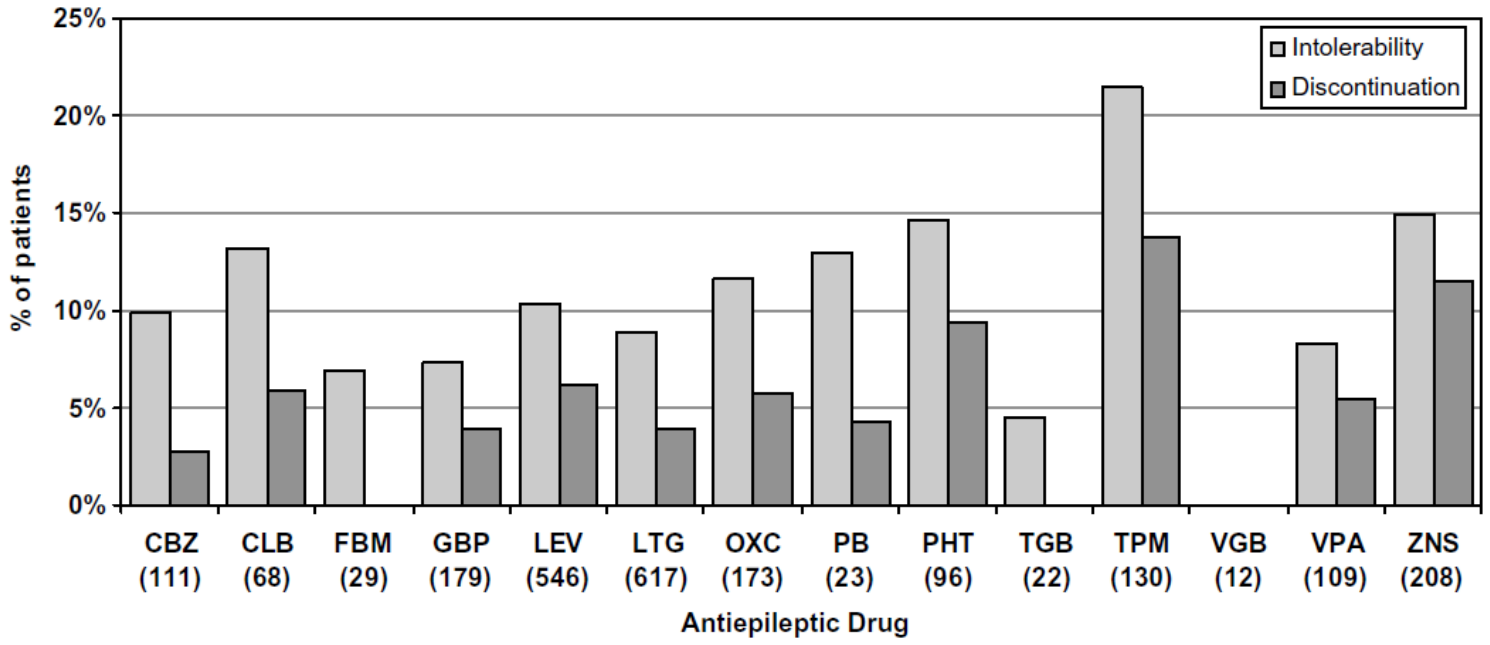
Seizure control

Treatment – antiepileptic drugs (AEDs)

Psychosocial environment

AEDs?

Intolerable cognitive side effects



Arif et al, Epilepsy and Behaviour, 2009

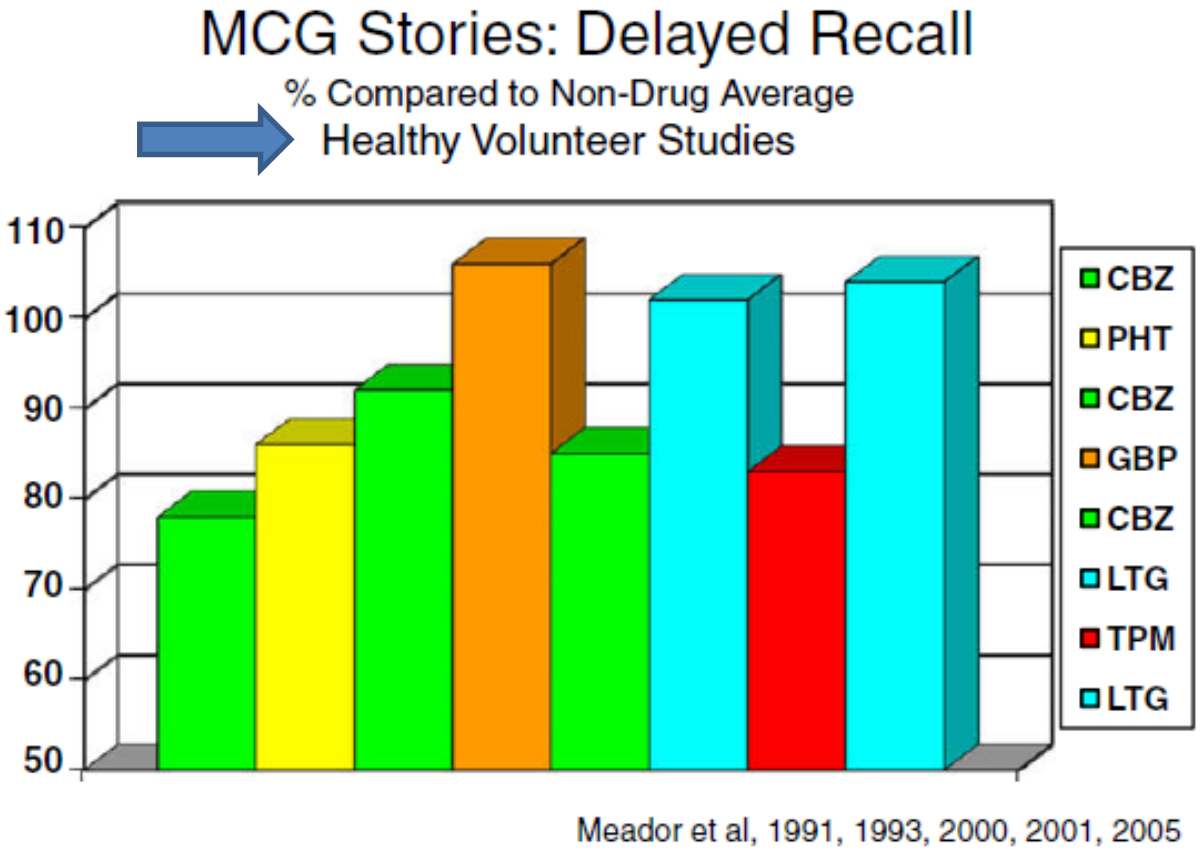
Studies in childhood epilepsy

Overview over the effects of common antiepileptic drugs on cognition.

	Attention		Psy.-mot. speed		Concentration		Memory		Language		Behavior	
	ad	ch	ad	ch	ad	ch	ad	ch	ad	ch	ad	ch
LTG	0	↑	0		0		0		0		↑	↑
LEV		↑	0				0				↑/↓	↓
TGB	0		0		0		0		0		0	
VGB	0		0		0		0		0			
FBM	(↓)											
GBP	0		0		↓	↓	0		0		(↑)	
ZNS	↓		0				(↓)		(↓)			
OXC	(↑)		↓/↑				0					↓
TPM	↓	↓	↓		↓	↓	↓		↓		(↓)	
CBZ			↓				↓	(↓)				
VPA	↓		↓				↓		0		↑/↓	↓
PB	↓		↓				↓			(↓)		
PHT	↓		↓		↓		↓	(↓)				
CLB	↓	↓	↓				0				↓	

↓: negative effect ; ↑ positive effect; () : possible effect; 0: no effect; blank: no evidence; ad: adults; ch: children.

Effects of AEDs on cognition



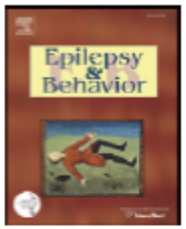
Meador et al, 1991, 1993, 2000, 2001, 2005

Epilepsy & Behavior 19 (2010) 55–64

Contents lists available at ScienceDirect

Epilepsy & Behavior

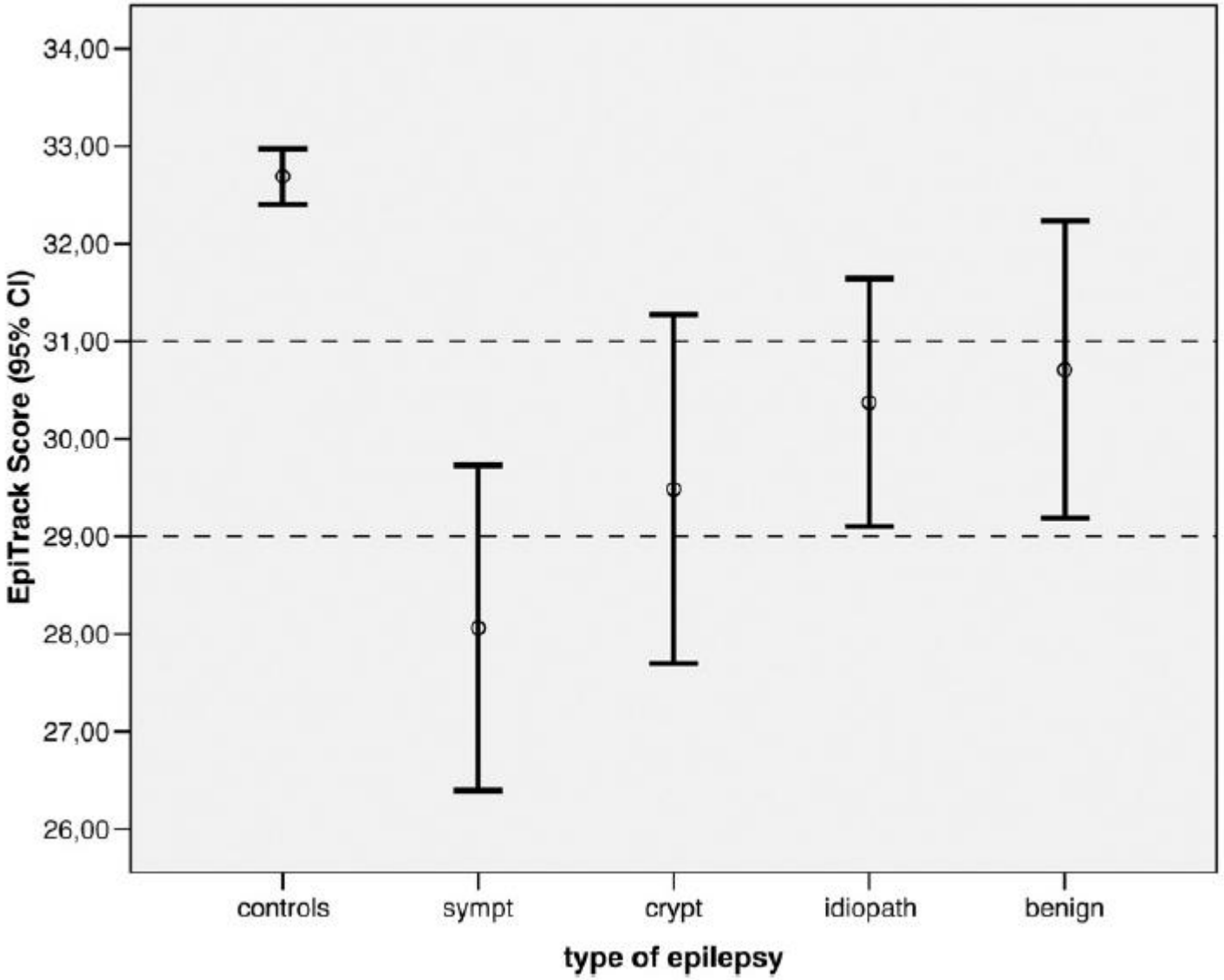
journal homepage: www.elsevier.com/locate/yebeh

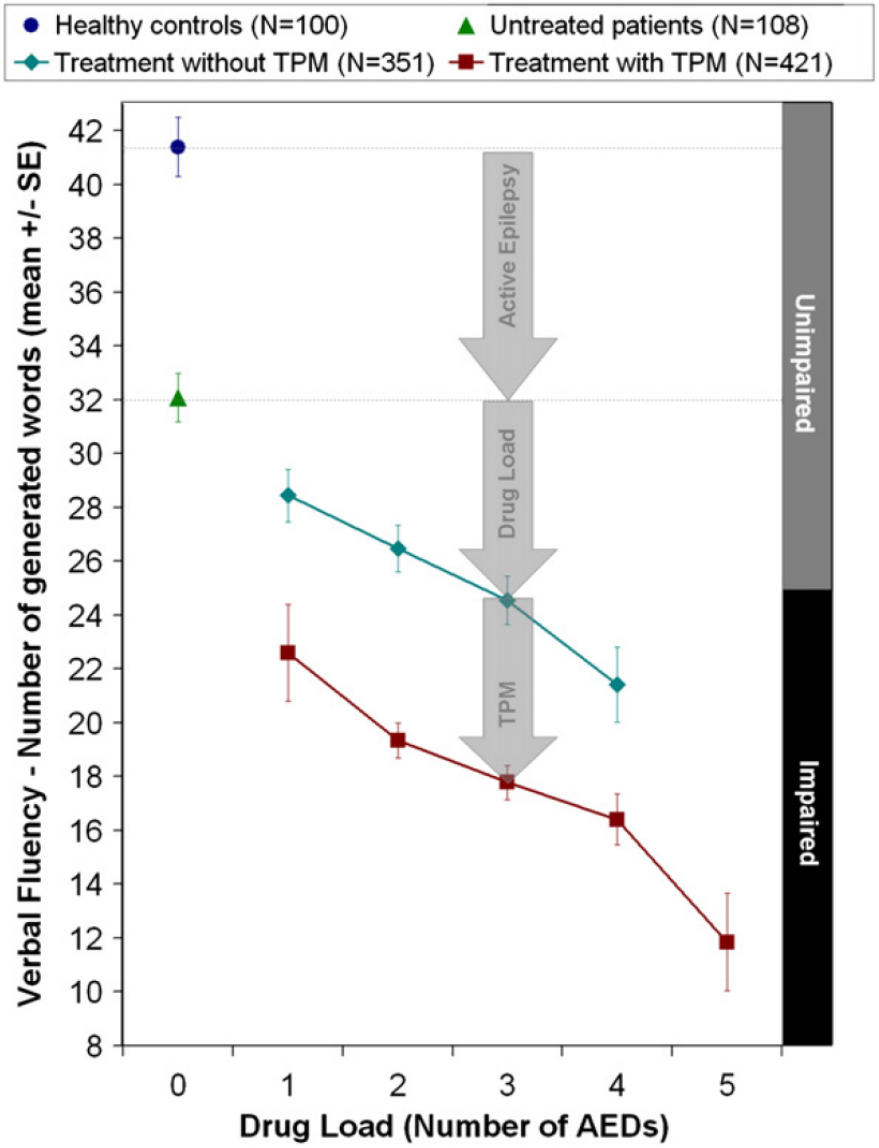


Introduction and first validation of EpiTrack Junior, a screening tool for the assessment of cognitive side effects of antiepileptic medication on attention and executive functions in children and adolescents with epilepsy

C. Helmstaedter [a,*], K. Schoof [a], T. Rossmann [b], G. Reuner [c], A. Karlmeier [d], G. Kurlemann [e]

[a] Department of Epileptology, University of Bonn, Bonn, Germany
[b] Department of Pediatrics, University of Vienna, Vienna, Austria
[c] Department of Pediatric Neurology, University of Heidelberg, Heidelberg, Germany
[d] Clinic for Neuropediatrics and Neurological Rehabilitation, BHZ Vogtareuth, Vogtareuth, Germany
[e] Department of Neuropediatrics, Children´s Hospital University Münster, Münster, Germany


34,00
33,00
32,00
31,00
30,00
29,00
28,00
27,00
26,00
EpiTrack Score (95% CI)
controls
sympt
crypt
idiopath
benign
type of epilepsy



Topiramate

verbal fluency

Witt and Helmstaedter, Epilepsy and Behaviour 2013

Summary : Cognitive dysfunctions in childhood epilepsy

Underlying aetiology (structural, genetic,...)

Seizure type, localization

Seizure frequency, severity

Epilepsy syndrome

EEG abnormalities

Seizure control

Treatment – antiepileptic drugs (AEDs)

Psychosocial environment

"All are equal, but some are more equal than others"

After G. Orwell