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Neurodevelopmental comorbidities in children:

the *ADHD example*

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Co-Morbidity
Definitions and Concepts

- Co-morbidity refers to the co-occurrence of two supposedly separate conditions that occur together more than by chance.

- In people with epilepsy, other conditions may **precede, co-occur with, or follow** the diagnosis of epilepsy.

Co-Morbidity
Definitions and Concepts

- Co-morbidities are not necessarily causal.
  - Both conditions may have a common biological substrate
  - An independent variable triggers one of the co-morbidities
    - Phenobarbital triggers depression
    - Vigabatrin triggers agitation

When defining co-morbidity of epilepsy

Co-morbidities

ADHD

Epilepsia, **46**(8):1333–1340, 2005
Blackwell Publishing, Inc.

Comment Letters

*Brian Neville
†Christopher Gillberg
**Paediatric Neurology*
†*Child and Adolescent Psychiatry*
The National Centre for Young People with Epilepsy
St. Piers Lane, Lingfield, Surrey
England

Comorbidity = any associated condition ?

- Caused by the primary pathogenesis of epilepsy;
- Caused by epilepsy itself (mesial temporal sclerosis; encephalopathy; behavior; etc.)
- Caused by epilepsy treatment
- Caused by social disadvantage.

Behavior and psychiatric problems

Co-morbidities

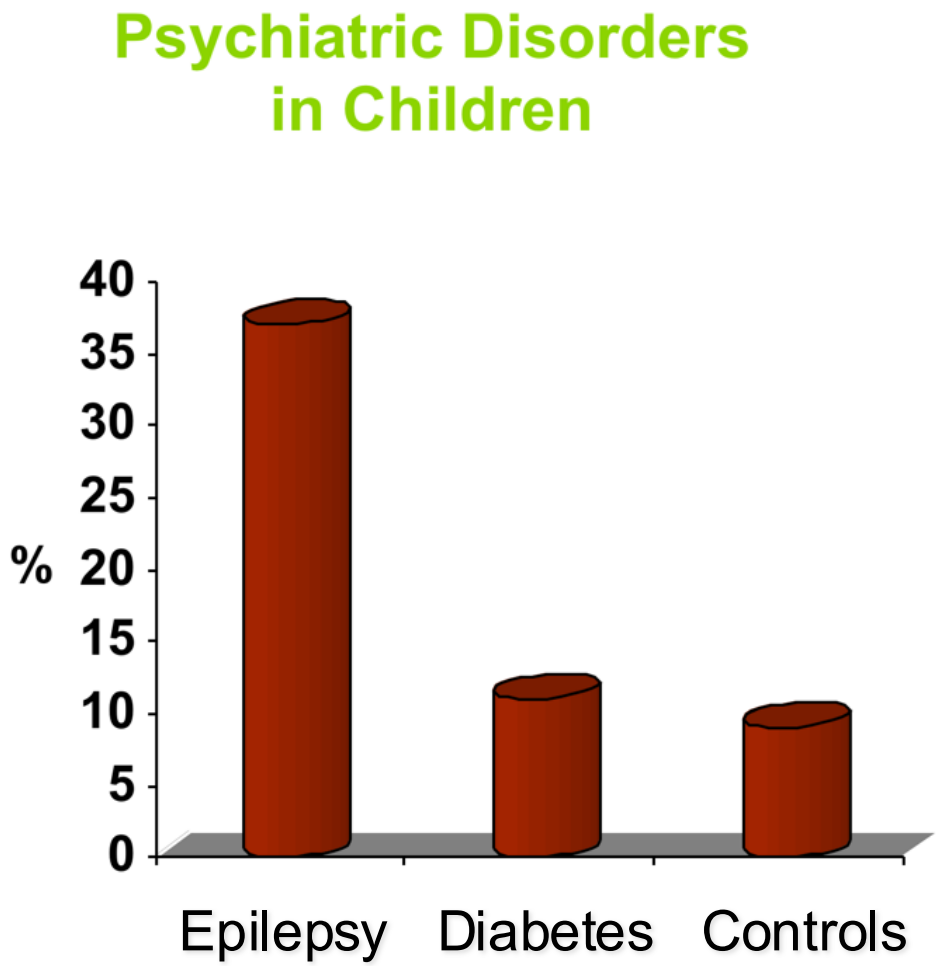
ADHD

- ADHD
- Autism
- Depression/Anxiety
- Psychosis
- Other behavior problems
  (ex. *aggressiveness*)
- Non epileptic seizures

Psychopathology and Epilepsy in Children

- Children with epilepsy are far more likely to suffer from a psychiatric disorder than children without epilepsy or with other chronic disorders.

- Emotional disorders, conduct disorders, attention, ADHD, depression, anxiety and autism spectrum disorder are over represented in children with epilepsy.



Davies et al., 2004

Behavioral and Emotional Problems In Children With Epilepsy

Problems

Rutter et al, 1970

Prevalence of Psychiatric Disorders in Adults and Children With Epilepsy

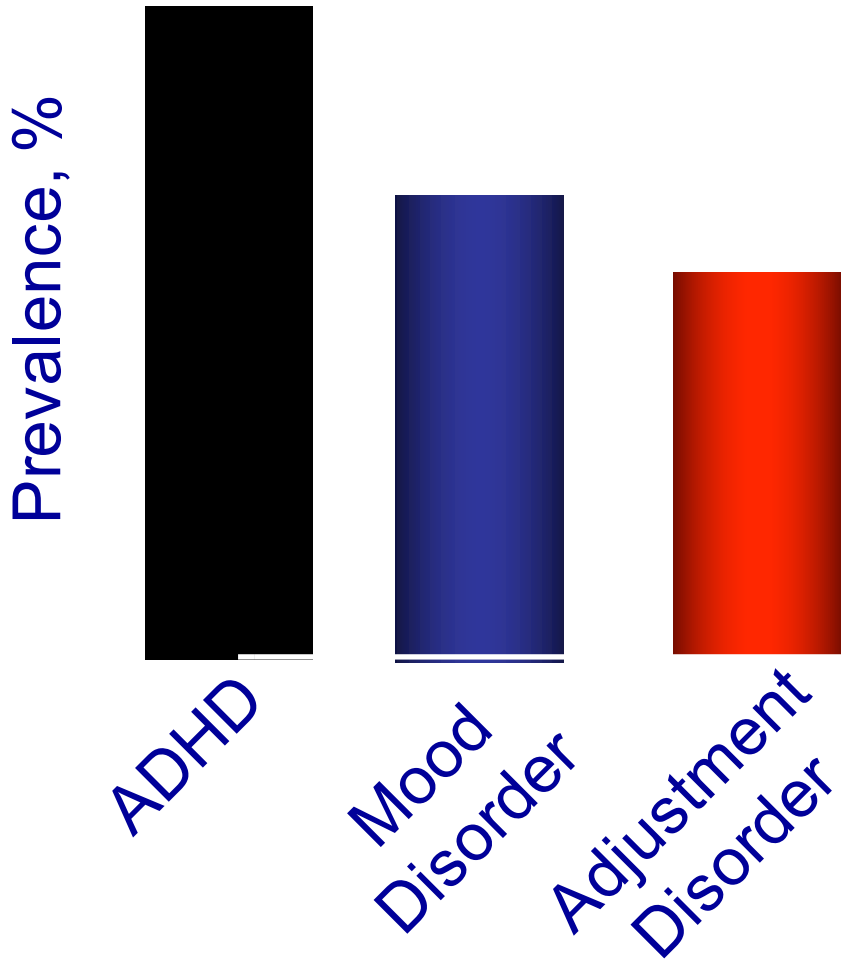
	Prevalence, %	
	Epilepsy Patients	General Population
Depression[1-4]	20-55	2-4
Anxiety/Panic Disorder[5-7]	19-45	2.5-6.5
Bipolar Disorder[8-9]	8-10	1-2
Psychosis[6,10]	2-8	0.5-0.7
ADHD[11-13]	15-35	2-10

The prevalence of each of these disorders is 10x that found in the general population.

[1]Kanner AM. *Biol Psychiatry*. 2003;54:388-398. [2]Ettinger A, et al. *Neurology*. 2004;63:1008-1014. [3]Wrench J, et al. *Epilepsia*. 2004;45:534-543. [4]Waraich P, et al. *Can J Psychiatry*. 2004;49:124-138. [5]Vazquez B, et al. *Epilepsy Behav*. 2003;4:S20-S25. [6]Kanner AM, et al. *Neurology*. 2004;62:708-713. [7]National Institute of Mental Health. NIH Publication No OM-02-4152. 2001. [8]Blum D, et al. In: Program and abstracts of the 54th Annual Meeting of the AAN; April 13-20, 2002. [9]Ettinger A, et al. *Neurology*. 2005;65:535-540. [10]Kendler KS, et al. *Arch Gen Psychiatry*. 1996;53:1022-1031. [11]Costello EJ. *J Am Acad Child Adolesc Psychiatry*. 1989. [12]Dunn DW, et al. *Dev Med Child Neurol*. 2003;45:50-54. [13]Kanner AM. *Epilepsia*. 2003;44(suppl 5):3-8.

Incidence of Psychiatric and Behavioral Comorbidities in **Adolescents**

- More than 50% of children with epilepsy evidence behavioral and psychiatric problems
- Retrospective analysis of patients diagnosed with childhood epilepsy identified ADHD, mood disorder, and adjustment disorder as the most common psychiatric manifestations



Hedderick et al. 2003

Attention Deficit Hyperactivity Disorder

- Children with epilepsy are at substantial risk for attention deficit/hyperactivity disorder (ADHD).

- Clinical studies suggest a prevalence of 30% to 40%, several fold higher than the normal population.

Dunn et al, 2003; Dunn and Kronenberger, 2005)

Attention Deficit Hyperactivity Disorder

Population-based case-control study (Iceland, < 16 years old).

ADHD, **inattentive type**, was 2.5 X more common in children with newly diagnosed seizures.

ADHD occurs more than expected **before** unprovoked seizures, suggesting common antecedent.

Hesdorffer et al, 2004

Attention Function & Epilepsy

Co-morbidities

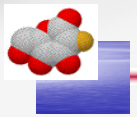
ADHD

Attention functions may also be affected by:

- Etiology of the epilepsy
- Duration of the epilepsy
- Type(s) of seizures
- History of prolonged Status Epilepticus
- Localization of the epileptogenic zone
- Treatment related (AED; dose; interactions)

Symptoms "mimicking" ADHD

AEDs may *exacerbate* or even *induce* ADHD-like symptoms



Co-morbidities

ADHD

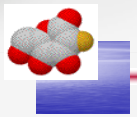
- Barbiturates and BZD have the most negative effects on attention and cognitive function;

- VPA may induce irritability.
In a recent trial of treatment for absence epilepsy, VPA had a more negative effect on attention than ethosuximide or lamotrigine.

- CBZ may induce 'variability', i.e. fluctuations, resembling attentional deficit, however only in regular (and not in slow release) form

Kwan & Brodie, 2001; Loring & Meador, 2004; Lagae 2006; Glauser 2010; B. Aldenkamp

AEDs may *exacerbate* or even *induce* ADHD-like symptoms



Co-morbidities

ADHD

- Of the newer antiepileptic drugs, **TPR** has more often caused concentration difficulty and cognitive slowing.

- LTG may induce hyperactivity in mentally retarded.

- LEV may induce hostility, resembling impulsivity;

Loring & Meador, 2004; Lagae 2006

AEDs may *exacerbate* or even *induce* ADHD-like symptoms

Antiepileptic drugs may contribute to problems with attention,
though **the relative effect of medication is probably significantly less than the adverse effect of seizures**

Occasional studies have found that polypharmacy had more adverse effect on attention than monotherapy.

Optimizing therapy of seizures in children and adolescents with ADHD

Albert P. Aldenkamp, PhD; Alexis Arzimanoglou, MD; Rianne Reijs, MD; and Saskia Van Mil, MA

Abstract—Attention deficit hyperactivity disorder (ADHD) can coexist with epilepsy and the prevalence of ADHD in epilepsy is three to five times greater than normal. This may be an effect of the epilepsy (particularly as a secondary symptom of subtle seizures) or of the antiepileptic treatment. There is an ongoing debate about the nature of ADHD in epilepsy and especially whether successive comorbidity exists (i.e., the possibility that epilepsy lowers the threshold for developing ADHD). Treatment of comorbid ADHD may be difficult. Methylphenidate is still the treatment of choice for the condition and, although it has been shown that neither methylphenidate nor other psychostimulants provoke seizures, there is still a possibility that seizure frequency may increase in children with active epilepsy.

NEUROLOGY 2006;67(Suppl 4):S49–S51

Give them a chance even in atypical cases with ADHD-like symptoms

Treatment of ADHD does not effect seizure threshold

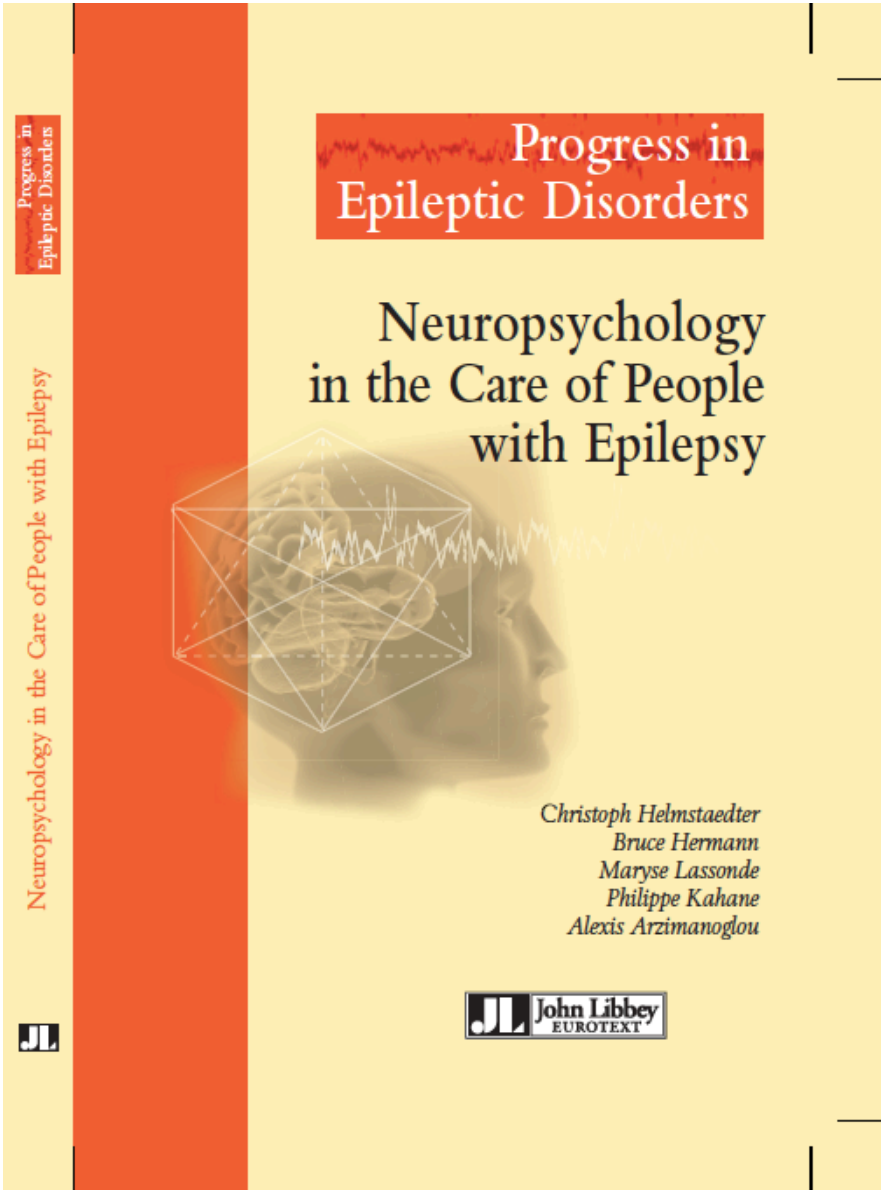
Courtesy G. Holmes

Neuropsychology in the Care of People with Epilepsy

Progress in Epileptic Disorders

Workshop (*) Toronto, Canada

November 2010



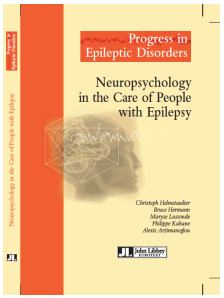
TAKE HOME MESSAGE

Recommendations—clinical

- Development of a **standard**, efficient, cost effective, and clinic/user-friendly **protocol for screening cognitive, behavioral, and academic status—preferably prior to initiation of AEDs**. Something that can be used widely (not just tertiary care based)
- Development of **core clinical information** to be collected at same time as above (e.g., screen for academic [and behavioral] difficulties).
- Development of **a standard of practice for treatment and referral** guidelines based on the above findings.
- Development of guidelines for re-administration of test battery to track medication effects, epilepsy course, and development.

Discussion

Christoph Helmstaedter, Bruce Hermann, Maryse Lassonde, Philippe Kahane, Alexis Arzimanoglou



What is the rational

- Early detection of pre-existing or progressively developing deficits, represent real challenges to the epilepsy teams wishing to develop global epilepsy-care programs.

- **Should every child with epilepsy undergo a systematic neuropsychological evaluation ?**

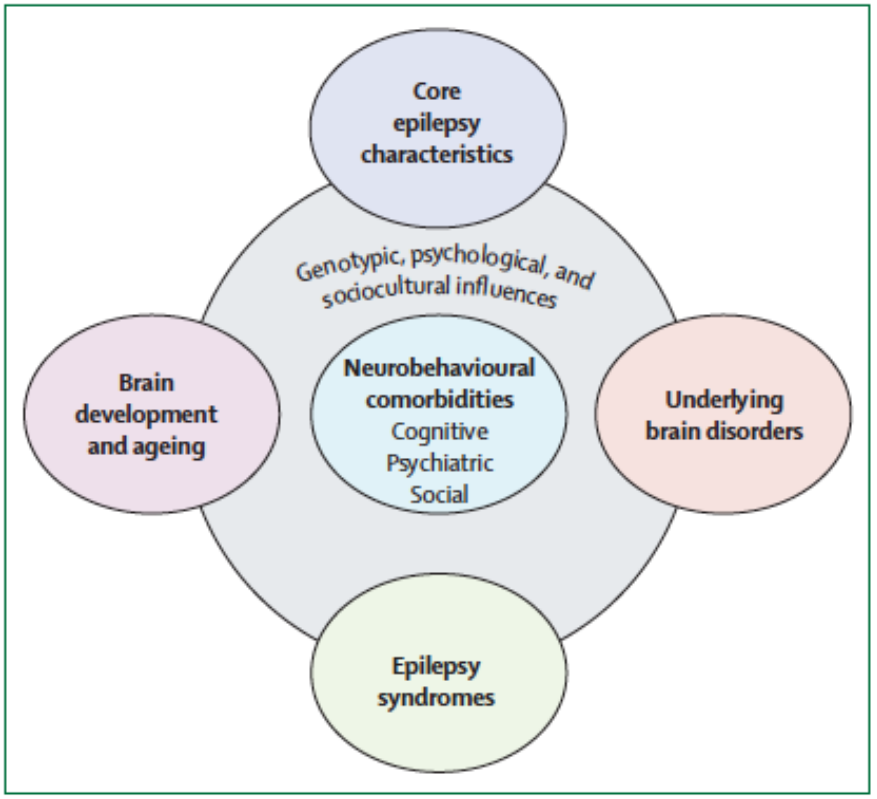


Figure 1: Major mediators of the neurobehavioral comorbidities of epilepsy

Development and validation of the Pediatric Epilepsy Side Effects Questionnaire

Neurology® 2012;79:1252-1258

3.5.	Questionnaire sur les éventuels effets indésirables du traitement antiépileptique observés LES 4 DERNIERES SEMAINES					
Effet indésirable en lien UNIQUEMENT avec les antiépileptiques en cours	Absence d'effet indésirable (1)	**Faible** sévérité de l'effet indésirable (2)	Sévérité **faible à moyenne** de l'effet indésirable (3)	Sévérité **moyenne** de l'effet indésirable (4)	Sévérité **moyenne à forte** de l'effet indésirable (5)	**Forte** sévérité de l'effet indésirable (6)
1. Ralentissement de la pensée						
2. Difficultés de mémoire						
3. Confusion						
4. Mauvais résultats scolaires						
5. Diminution de la concentration						
6. Difficultés d'attention						
7. Instabilité de la marche						
8. Maladresse. Mauvaise coordination.						
9. Chutes (autres que des crises d'épilepsie)						
10. Difficultés à parler						
11. Agressivité						
12. Hyperactivité						
13. Changement de personnalité						
14. Somnolence						
15. Fatigue						
16. Vertiges						
17. Maux de tête						
18. Hausse de l'appétit						
19. Prise de poids						
20. Perte de l'appétit						
21. Perte de poids						