ADHD
nei Servizi di Neuropsichiatria in Italia

La Comorbilità nell'ADHD

Milano, 14 dicembre 2016
10.00-18.00

15 dicembre 2016
9.00-18.00 - AULA A

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Istituto di Ricerche Farmacologiche Mario Negri
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FONDAZIONE PTV
POLICLINICO TOR VERGATA

La Comorbilità nell'ADHD
Disturbi a bassa Frequenza
Epilessia

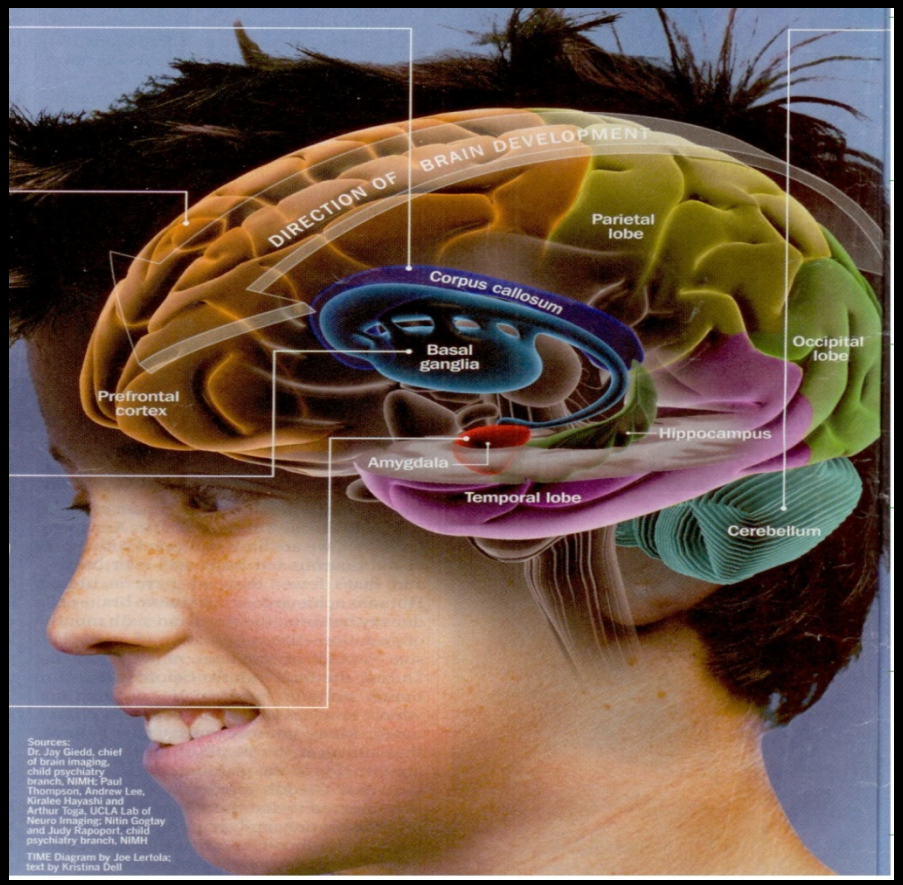
Caterina Cerminara
Neuropsichiatra Infantile

UNIVERSITA' degli STUDI di ROMA TOR VERGATA

PREVALENCE OF ADHD IN CHILDREN WITH EPILEPSY

- The prevalence of ADHD in children with Epilepsy has been observed to in the range of 12 to 39%

- ADHD Inattentive Subtype 24%
- ADHD Combined Subtype 11%
- ADHD Hyperactive/Impulsive Subtype 2%



PREVALENCE OF ADHD IN CHILDREN WITH EPILEPSY

- 12% of 25 children with “complicated” Epilepsy +ADHD
  2.1% of children with diabetes + ADHD
  None of 42 children with “uncomplicated” Epilepsy had -ADHD
  Davies,2003

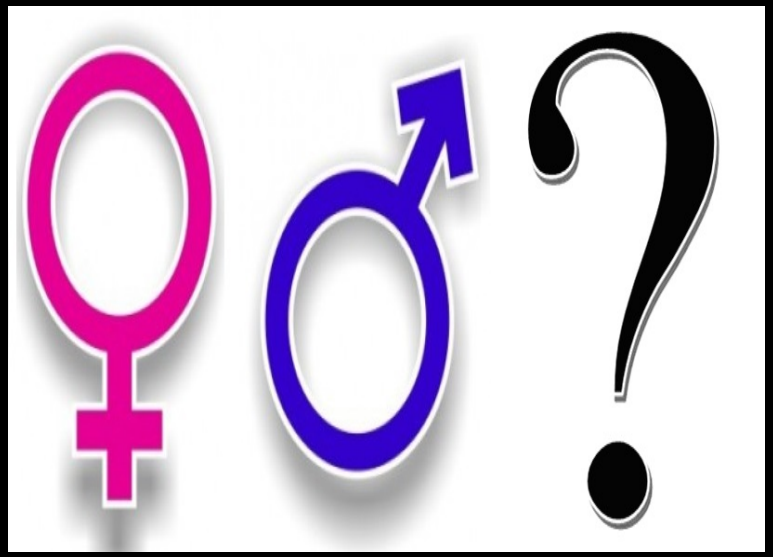
- 13,7% of the children with Epilepsy + ADHD
  Hesdorffer, 2004

- 28,1% of children with Epilepsy + “Hyperactivity”
  5.7 times higher control children
  2.3 times higher control children with cardiac problem
  Mcdermott, 1995

- 17% of 134 children (medical records) with Epilepsy + ADHD
  Hedderick and Buchhalter, 2003

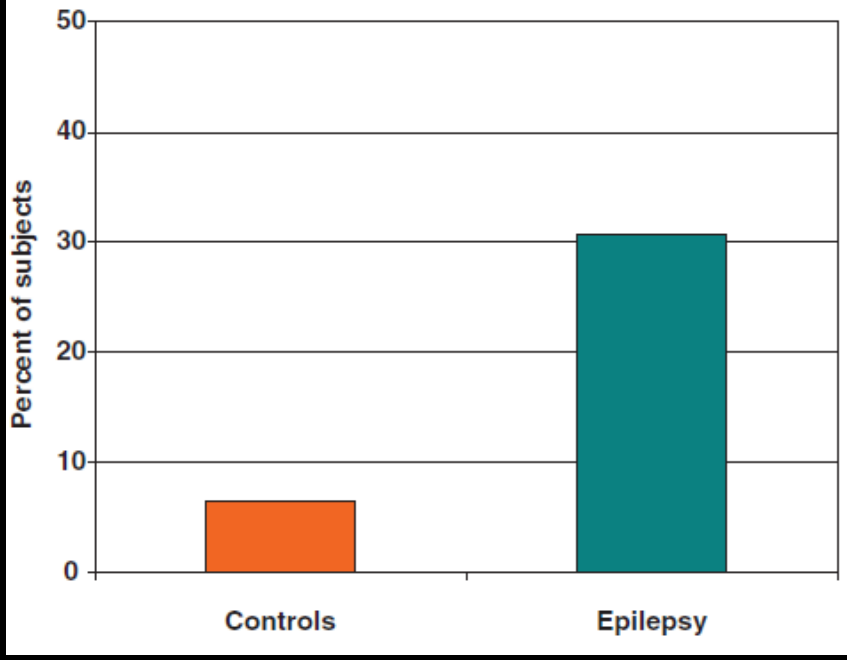
PREVALENCE OF ADHD IN CHILDREN WITH EPILEPSY

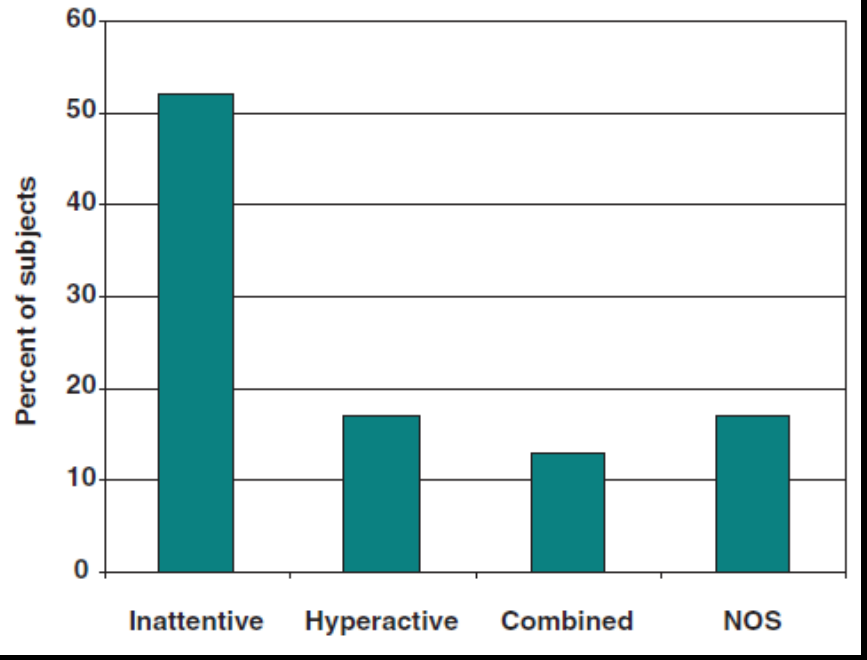
Without Epilepsy, ADHD is seen in school-aged children with a Male to Female Ratio of 2-3:1



ADHD + EPILEPSY the Ratio is 1:1

ADHD IN CHILDREN WITH EPILEPSY





TIMING OF ADHD AND ITS COMORBIDITIES: *"Care was taken to date the onset of ADHD in relation to the first-recognized seizure and the diagnosis of epilepsy. Both ADHD and its complications antedatted the diagnosis of epilepsy in tha majority of cases (82% for ADHD, 65% for academics; n 75)"*

ADHD as a Risk Factor for Incident Unprovoked Seizures and Epilepsy in Children

Dale C. Hesdorffe
Olafur Kjartansso

Table 2. Attention-Deficit/Hyperactivity Disorder as a Risk Factor for Incident Unprovoked Seizure in Icelandic Children

Diagnosis	No. of Cases	No. of Controls	Odds Ratio* (95% Confidence Interval)
Whole group (109 cases and 218 controls)			
ADHD-I	7	4	3.7 (1.1-12.8)
ADHD-H	6	7	1.8 (0.6-5.7)
ADHD-C	2	2	2.5 (0.3-13.3)
ADHD	15	13	2.5 (1.1-5.5)
Referent	94	205	1.0 (Referent)
Partial onset (56 cases and 112 controls)†			
ADHD-I	3	1	5.2 (0.5-50.4)
ADHD-H	4	5	1.7 (0.4-7.0)
ADHD-C	0	2	NA
ADHD	7	8	1.9 (0.6-5.9)
Referent	49	104	1.0 (Referent)
Generalized onset (52 cases and 104 controls)†			
ADHD-I	4	3	2.7 (0.6-11.9)
ADHD-H	1	2	1.0 (0.1-11.0)
ADHD-C	2	0	NA
ADHD	7	5	2.8 (0.9-8.8)
Referent	45	99	1.0 (Referent)
Idiopathic/cryptogenic (97 cases and 194 controls)			
ADHD-I	4	4	2.1 (0.5-8.6)
ADHD-H	6	6	2.2 (0.7-7.2)
ADHD-C	2	2	2.2 (0.3-16.2)
ADHD	12	12	2.2 (0.9-5.0)
Referent	85	182	1.0 (Referent)
Remote symptomatic (12 cases and 24 controls)			
ADHD-I	3	0	NA
ADHD-H	0	1	NA
ADHD-C	0	0	NA
ADHD	3	1	6.0 (0.6-57.7)
Referent	9	23	NA
Epilepsy (64 cases and 128 controls)			
ADHD-I	5	2	5.0 (1.0-25.8)
ADHD-H	4	4	2.3 (0.5-10.4)
ADHD-C	1	1	2.0 (0.1-32.0)
ADHD	10	7	3.1 (1.1-8.6)
Referent	54	121	1.0 (Referent)
Single unprovoked seizure (45 cases and 90 controls)			
ADHD-I	2	2	2.3 (0.3-17.7)
ADHD-H	2	3	1.3 (0.2-8.0)
ADHD-C	1	1	2.6 (0.1-45.9)
ADHD	5	6	1.7 (0.5-6.2)
Referent	40	86	1.0 (Referent)

2.5-fold increased risk for unproked seizures in children with ADHD

3.7 fold increased risk for unproked seizures in children with ADHD-I

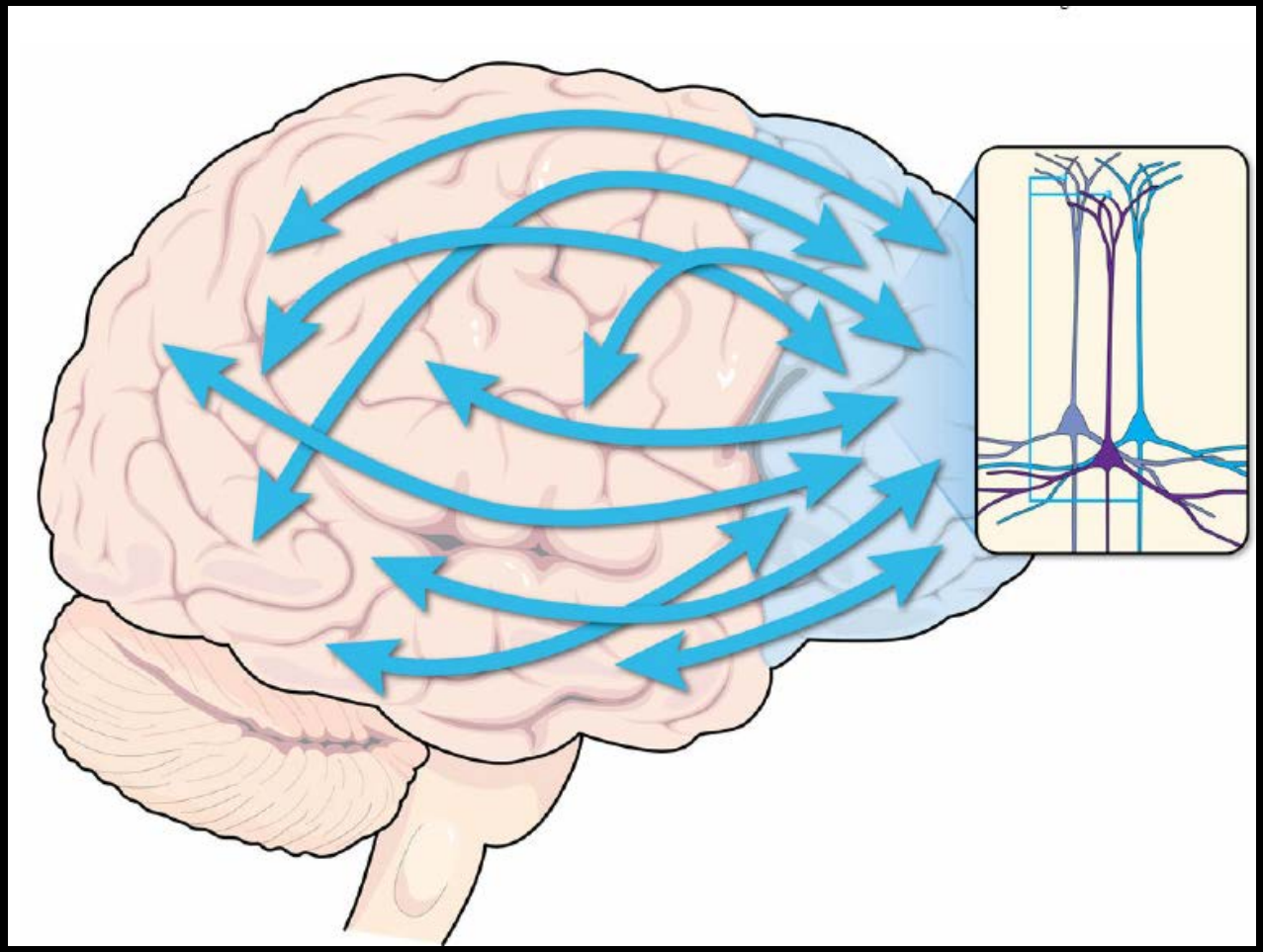
Hesdorffer DC, 2004

Catecholamine Influences on Prefrontal Cortical Function: Relevance to Treatment of Attention Deficit Hyperactivity Disorder and Related Disorders

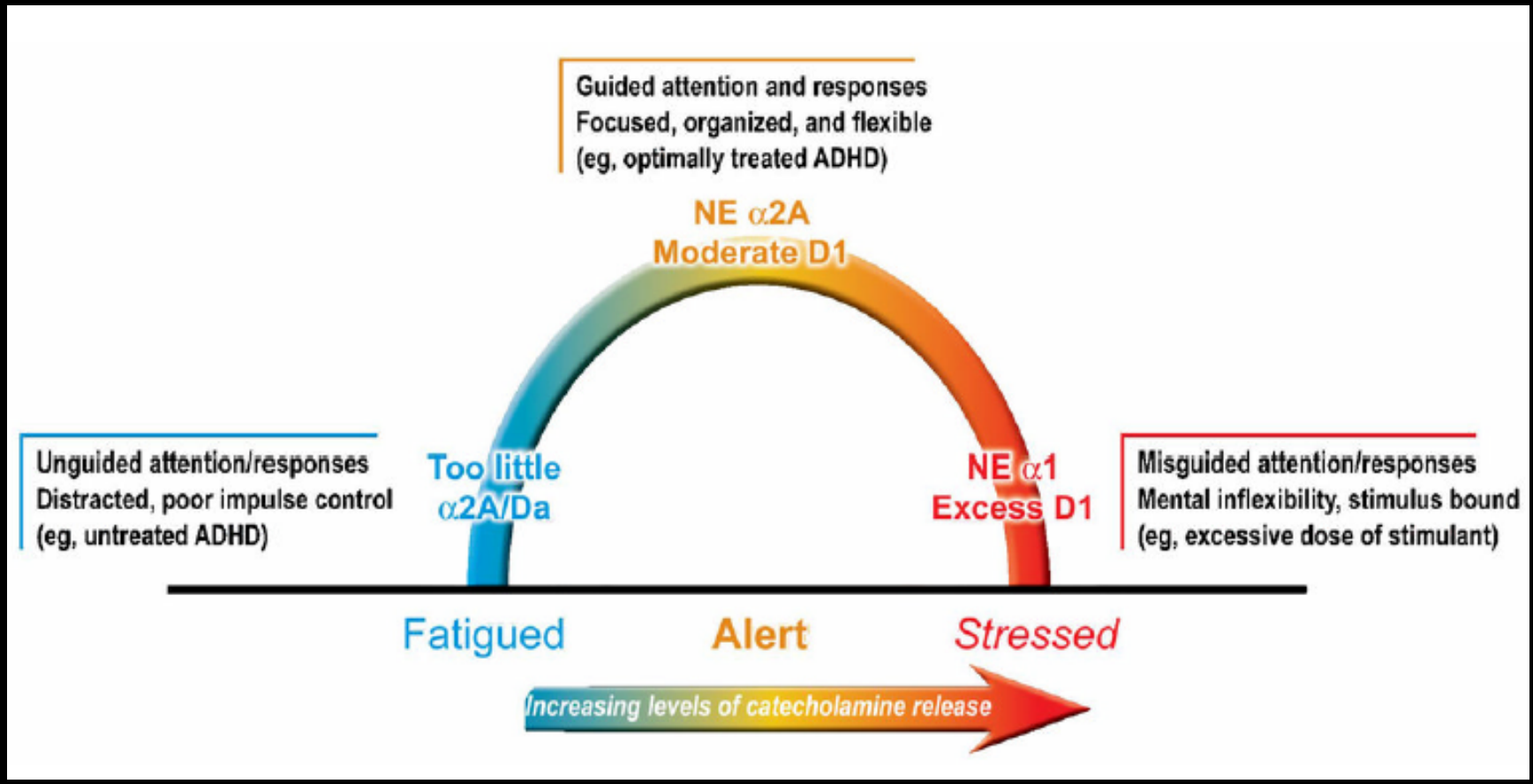
Amy F. T. Arnsten, PhD[1] and **Steven R. Pliszka, MD**[2]

[1]Department of Neurobiology, Yale University School of Medicine, New Haven, CT, USA

[2]Department of Psychiatry, University of Texas Health Science Center, San Antonio, TX, USA



Amy, 2011


Guided attention and responses
Focused, organized, and flexible
(eg, optimally treated ADHD)
NE α2A
Moderate D1
Unguided attention/responses
Distracted, poor impulse control
(eg, untreated ADHD)
Too little
α2A/Da
NE α1
Excess D1
Misguided attention/responses
Mental inflexibility, stimulus bound
(eg, excessive dose of stimulant)
Fatigued
Alert
Stressed
Increasing levels of catecholamine release

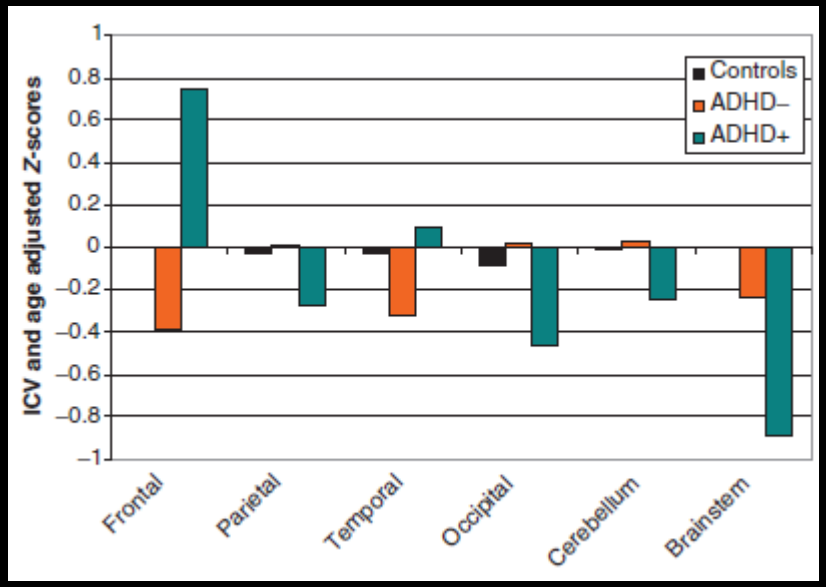
Amy, 2011

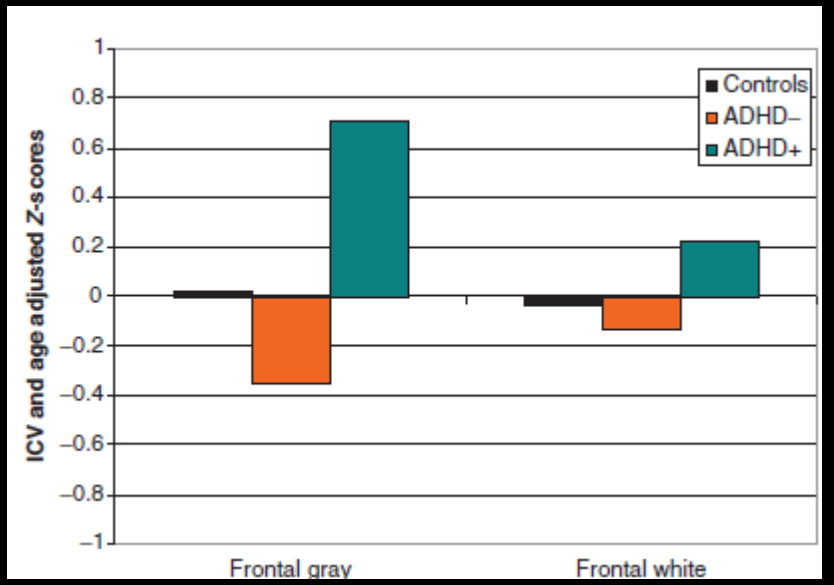
ADHD-Epilepsy Comorbidity: the Neurobiology

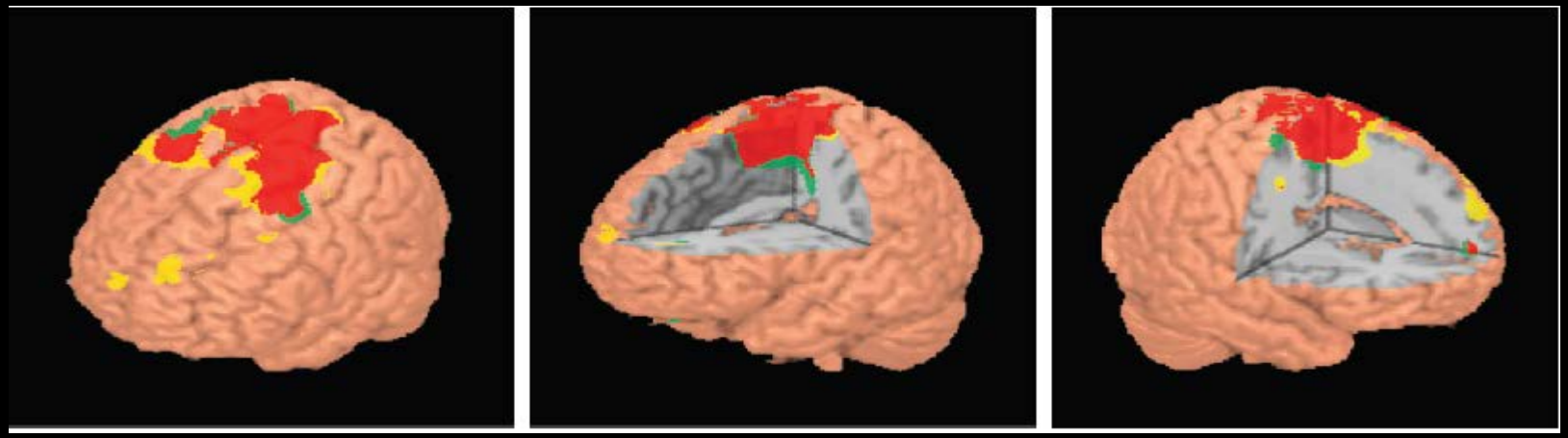
- Quantitative MRI demonstrated that ADHD in epilepsy is associated with significantly increased grey matter in the frontal lobe and significant smaller brainstem volume

- Animal models of ADHD suggest that synaptic abnormality in excitatory glutamatergic transmission may contribute to vulnerability for epilepsy and ADHD, and could help to identify common pathophysiological events between these two conditions

Brain Morfology in Children with Epilepsy and ADHD







Hermann, 2007

ADHD and Epilepsy types

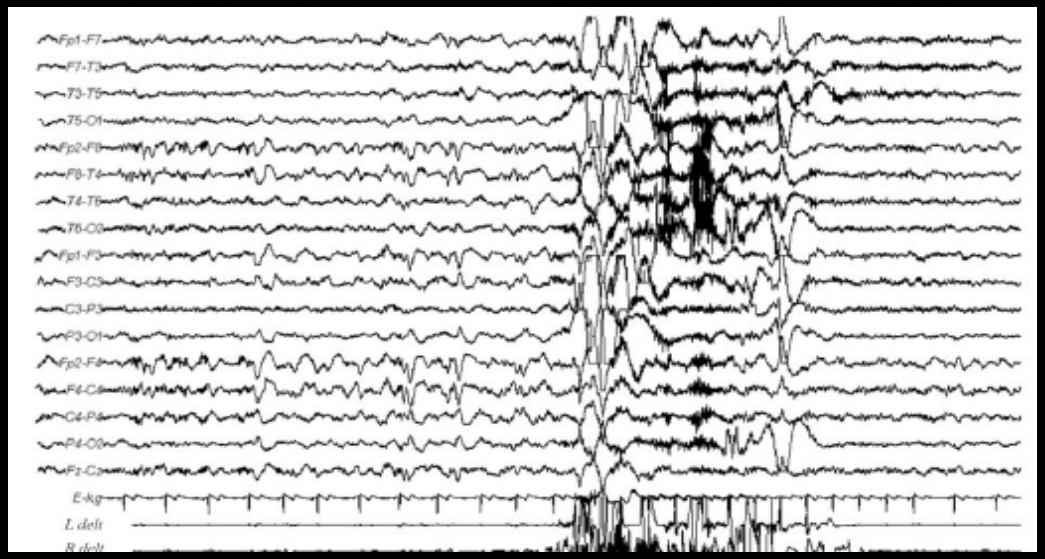
- Certain epilepsy syndromes may predispose to ADHD-like behavior
- Patients who have generalized epilepsies are more frequently reported to have attentional difficulties than patients suffering from partial seizures.
- The presence of ADHD symptoms at the time of epilepsy onset is a major marker of abnormal cognitive development

Dunn, 2015

ADHD and Frontal Lobe Epilepsy

- FLE shares behavioral features with ADHD, presenting in some patients with impulsivity, disinhibition, and excitement/irritability

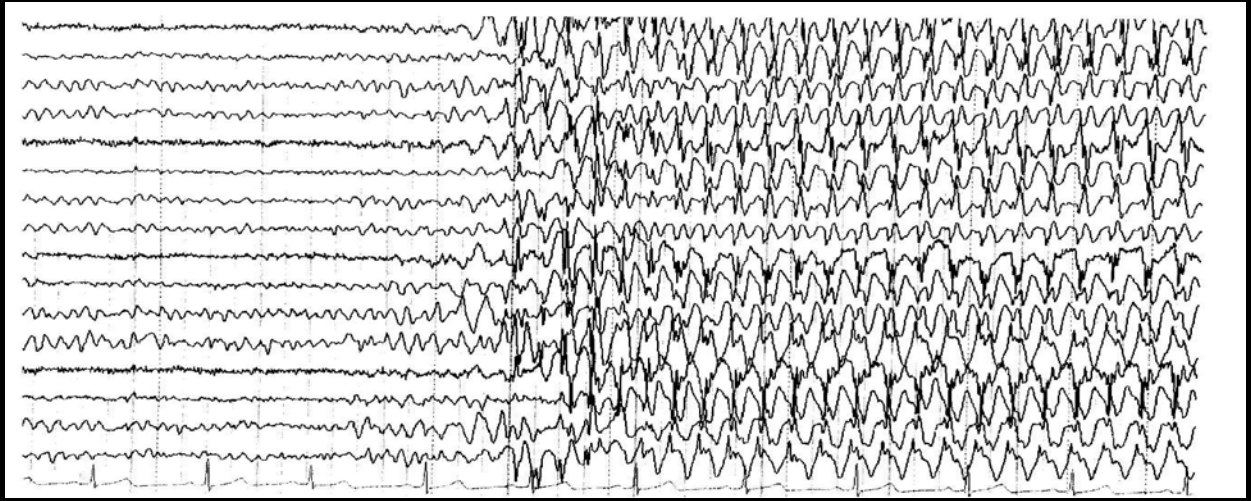
- There is a critical early stage of brain maturation during which frontal lobes EEG discharges perturb the development of brain system underpinning attention and hyperactive disorders, therefore interfering with the normal development of learning processes



Prevost 2006

ADHD and “Benign” Epilepsies

- Childhood absence epilepsy
  - Children affected by CAE have difficulty in visual sustained attention, verbal and non-verbal attention, and memory, despite a good response to AEDs and normal intelligence
  - ADHD is the most common psychiatric diagnosis in children affected by CAE, with a prevalence of the inattentive subtype



Barnes, 2008

ADHD and “Benign” Epilepsies

- Rolandic epilepsy
  - Rolandic spikes are clearly more frequent in ADHD children than in the general pediatric population, even if there is still no clear explanation for this association
  - Children suffering from benign epilepsy with centro-temporal spikes have been shown to have a greater susceptibility to distracters occurring in their visual field compared to healthy children and children affected by idiopathic generalized epilepsies

Deltour , 2007

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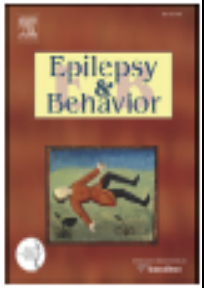

Brief Communication

Attention impairment in childhood absence epilepsy: An impulsivity problem?

Caterina Cerminara [a,*,1], Elisa D'Agati [a,1], Livia Casarelli [a], Ivo Kaunzinger [b], Klaus W. Lange [b], Mariabernarda Pitzianti [a], Pasquale Parisi [c], Oliver Tucha [d], Paolo Curatolo [a]

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[b] Department of Experimental Psychology, University of Regensburg, Germany
[c] Paediatric Department, II Faculty of Medicine, University of Rome "La Sapienza", Italy
[d] Department of Clinical and Developmental Neuropsychology, University of Groningen, The Netherlands

- 12 boys-12 girsl with CAE and seizure-free
- Age 8-14
- IQ>80,
- EEG with bilateral symmetrical and synchronous spike and-wave at 3 Hz
- 18 with VPA, 4 with LEV, 1 with LTG, 1 with VPA+LTG,, 1 with VPA+LEV
- No ADHD and psychiatric disorders and neurological impairments

Test performance of patients with absence epilepsy compared to control children (mean + SD).

	Healthy children N = 24	Children with absence epilepsy N = 24	Z	p
Intensity of attention				
Tonic arousal (tonic alertness task)				
Reaction time (ms)	300.77 ± 45.83	335.15 ± 101.63	−0.46	.648
Variability of reaction time (ms)	40.03 ± 17.63	69.98 ± 58.93	−2.77	.006*
Number of omission errors	0.04 ± 0.20	0.13 ± 0.45	−1.00	.317
Phasic arousal (phasic alertness task)				
Reaction time (ms)	287.08 ± 47.89	309.17 ± 68.30	−1.10	.271
Variability of reaction time (ms)	50.23 ± 32.26	90.12 ± 72.80	−2.63	.009*
Number of omission errors	0.29 ± 0.55	0.13 ± 0.34	−1.41	.157
Vigilance (vigilance task)				
Reaction time (ms)	809.15 ± 149.65	751.98 ± 137.44[a]	−0.96	.338
Variability of reaction time (ms)	178.24 ± 64.89	174.64 ± 71.24[a]	−0.06	.951
Number of commission errors	4.46 ± 3.72	6.87 ± 7.09[a]	−1.95	.051
Number of omission errors	5.21 ± 4.11	6.13 ± 3.61[a]	−0.52	.603
Selectivity of attention				
Divided attention (divided attention task)				
Reaction time (ms)	805.60 ± 86.73	786.81 ± 113.50	−0.29	.775
Variability of reaction time (ms)	280.00 ± 87.73	321.59 ± 95.49	−1.34	.179
Number of commission errors	2.50 ± 2.38	4.21 ± 4.52	−1.12	.264
Number of omission errors	4.04 ± 3.37	7.21 ± 3.73	−3.79	.001*
Impulsivity (Go/No-Go task)				
Reaction time (ms)	634.44 ± 80.63	666.67 ± 110.40	−1.53	.126
Variability of reaction time (ms)	91.45 ± 23.92	132.94 ± 73.71	−2.74	.006*
Number of commission errors	0.63 ± 1.01	2.67 ± 4.05	−3.38	.001*
Number of omission errors	0.04 ± 0.20	1.00 ± 2.45	−2.20	.028
Focused attention (incompatibility task)				
Reaction time (ms)	556.17 ± 127.44	533.56 ± 153.51	−1.06	.290
Variability of reaction time (ms)	156.62 ± 80.71	193.89 ± 146.62	−0.51	.607
Number of commission errors	7.88 ± 7.17	10.08 ± 9.19	−1.06	.291
Selective attention (visual scanning task)				
Reaction time (ms)	4215.67 ± 1578.28	3179.81 ± 1468.43	−2.89	.004*
Variability of reaction time (ms)	2317.58 ± 1160.52	1938.79 ± 958.09	−1.29	.199
Number of commission errors	0.58 ± 1.10	1.08 ± 2.38	−0.78	.437
Number of omission errors	3.96 ± 2.16	6.17 ± 4.04	−2.39	.020

The patients with CAE were marked impaired in some measures of Alertness, Diveded Attention, Impulsivity and Selective Attention

The higher rate of commission errors and false positive answers of this patients indicates problems in controlling behavior in the Go/No-Go task in the impulsivity task.

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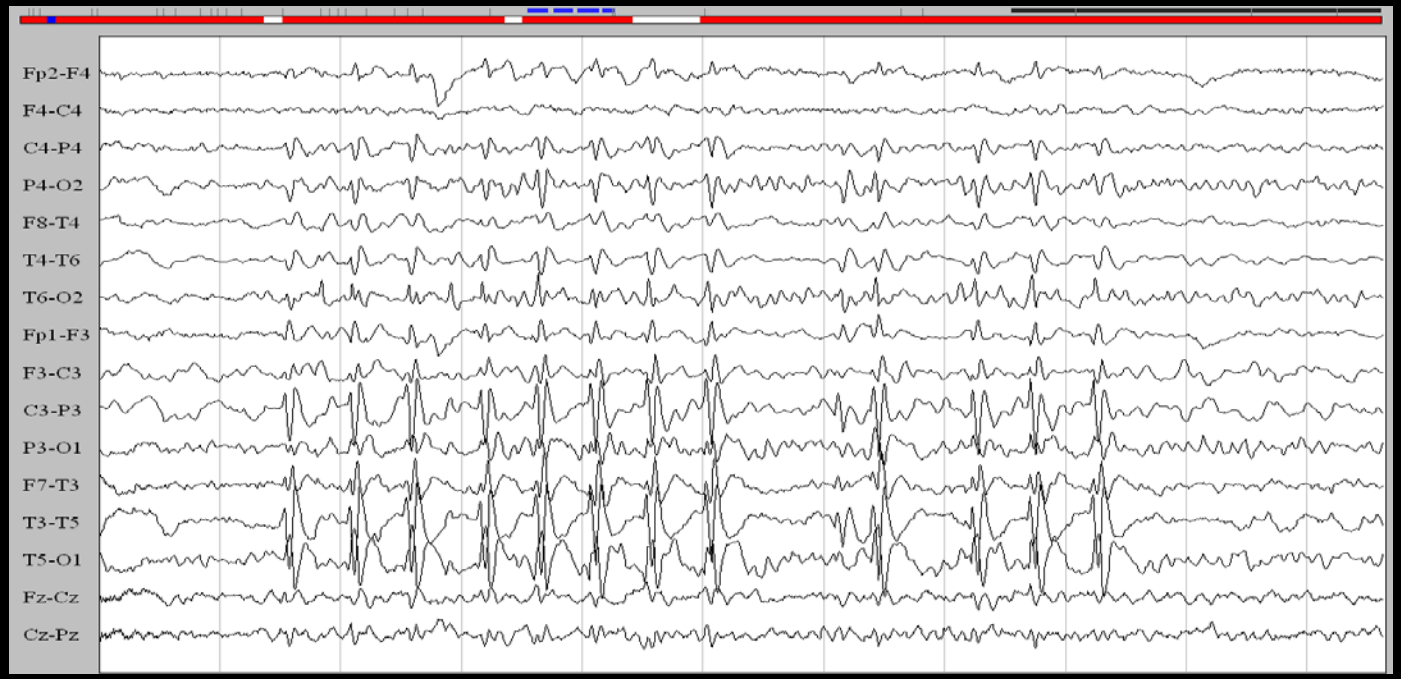
Benign childhood epilepsy with centrotemporal spikes and the multicomponent model of attention: A matched control study

Caterina Cerminara [a,*], Elisa D'Agati [a], Klaus W. Lange [b], Ivo Kaunzinger [b], Oliver Tucha [c], Pasquale Parisi [d], Alberto Spalice [e], Paolo Curatolo [a]

Characteristics of patients with rolandic epilepsy and matched healthy participants.

	Ro/Co[a]	Ro-EO/ Co-EO	Ro-LO/ Co-LO	Ro-HSI/ Co-HSI	Ro-LSI/ Co-LSI
N (each group)	21	9	12	11	9
Sex (F/M)	9/12	3/6	6/6	6/5	3/6
Age (years)	$9.86 \pm 1.59_b$	9.22 ± 1.64	10.33 ± 1.43	9.45 ± 1.44	10.33 ± 1.80



- All partecipants were tested with a computerized test battery that consisted of a:
- selective attention task
- Impulsivity task
- Focused Attention task
- Vigilance task

Results

- Impairment in Selectivity (Impulsivity, Focused Attention, Selective Attention, Aspects of Divided Attention)
- Impaireant in Intensity (Arousal), No impairment in Vigilance
- No correlation with electroclinical variables of age at onset and spike index on sleep EEGs

Pharmacological Treatment in ADHD+ Epilepsy

- Safety: any tendency to increase the likelihood of seizures and interactions with AEDs
- Tolerability: as children with epilepsy appear to have higher rates of side effects or adverse reactions other than seizures
- Efficacy: pharmacological trials

Torres, 2008

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Methylphenidate improves the quality of life of children and adolescents with ADHD and difficult-to-treat epilepsies

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ABSTRACT

Objective: Comorbidity between difficult-to-treat epilepsies and ADHD is frequent and impacts negatively on quality of life. The commonly held (yet poorly substantiated) view that stimulants may worsen seizure control has prevented studies from evaluating the impact of such treatment in this population. Our aim was to study the effect of methylphenidate on the quality of life of children and adolescents with difficult-to-treat epilepsies and comorbid ADHD.

Methods: The study was an open-label, noncontrolled trial with intention-to-treat analysis following 30 patients for 6 months. Subjects received methylphenidate following 3 months of baseline, during which antiepileptic drugs (AEDs) were adjusted and epilepsy, ADHD, and quality-of-life variables were assessed. Multivariate regression analysis identified the main variables correlated with outcome.

Results: Only one patient withdrew because of seizure worsening. Following methylphenidate introduction, doses were titrated up to 0.40–0.50 mg/kg/day. A marked improvement in quality-of-life scores and a significant reduction in seizure frequency and severity were observed. Female sex, reduction of core ADHD symptoms, and tolerability to adequate doses of methylphenidate were significantly associated with improved quality-of-life scores.

Conclusion: These preliminary data suggest that methylphenidate treatment is safe and effective in patients with ADHD and difficult-to-treat epilepsies, positively impacting on quality-of-life scores.

ADHD in childhood epilepsy: Clinical determinants of severity and of the response to methylphenidate

[1,2]Sylvain Rheims, [2,3]Vania Herbillon, [4]Nathalie Villeneuve, [5]Stéphane Auvin, [6]Silvia Napuri, [7]Claude Cances, [8]Patrick Berquin, [9]Pierre Castelneau, [10]Sylvie Nguyen The Tich, [11]Frédéric Villega, [12]He [14]Behrouz Kassai, [2,3]A

Table 1. Patients' baseline clinical characteristics

	All patients	Patients followed without specific pharmacologic intervention for ADHD	Patients in whom MPH was initiated at study entry
Total, n (%)	167	106 (63)	61 (37)
Age, mean ± SD	9.5 ± 2.4	9.5 ± 2.3	9.6 ± 2.4
Gender (boys), n (%)	112 (67)	74 (70)	38 (62)
Epilepsy			
Syndrome, n (%)			
Nonidiopathic focal epilepsy	50 (30)	36 (34)	14 (23)
Idiopathic focal epilepsy	46 (28)	28 (26)	18 (30)
Childhood absence epilepsy	27 (16)	11 (10)	16 (26)
Other forms of genetically determined generalized epilepsies	26 (16)	21 (20)	5 (8)
Others	14 (8)	7 (7)	7 (11)
Unavailable	4 (2)	3 (3)	1 (2)
Age at epilepsy onset, mean ± SD	5.0 ± 3.3	4.8 ± 3.3	5.3 ± 3.2
Active epilepsy, n (%)	76 (46)	48 (45)	28 (46)
Number of ongoing AED, n (%)			
0	36 (22)	21 (20)	15 (25)
1	86 (52)	57 (54)	29 (47)
2	38 (22)	21 (20)	17 (28)
≥3	7 (4)	7 (6)	0
AED, n (%)			
Sodium valproate	69 (41)	46 (43)	23 (38)
Lamotrigine	25 (15)	12 (12)	12 (20)
Ethosuximide	13 (8)	9 (8)	4 (7)
Topiramate	3 (2)	2 (2)	1 (2)
Carbamazepine/oxcarbazepine	27 (16)	19 (18)	8 (13)
Benzodiazepines	19 (11)	14 (13)	5 (8)
Levetiracetam	19 (11)	12 (11)	7 (12)
Other	8 (5)	6 (6)	2 (3)
School performance, n (%)			
History of repeating grades	57 (35)	35 (33)	22 (37)
Parental estimation of school performances			
Very good/good	39 (23)	26 (24)	13 (21)
Intermediate	65 (39)	44 (42)	21 (34)
Insufficient/very insufficient	63 (38)	36 (34)	27 (44)
Specific educational program			
Yes	11 (6)	10 (1)	1 (2)
No	156 (94)	96 (99)	60 (98)
ADHD			
Type, n (%)			
ADHD-I	68 (43)	42 (42)	26 (44)
ADHD-C	92 (57)	59 (58)	33 (56)
Age at ADHD onset, mean ± SD	5.4 ± 1.9	5.3 ± 1.8	5.6 ± 2.1
ADHD Rating Scale-IV, mean ± SD			
Total score	30.4 ± 9.2	29.3 ± 8.4	32.4 ± 10.2
Inattentive subscore	17.3 ± 4.4	16.7 ± 4.1	18.1 ± 4.8
Hyperactivity subscore	13.2 ± 6.6	12.4 ± 6.2	14.3 ± 7.2

ADHD in childhood epilepsy: Clinical determinants of severity and of the response to methylphenidate

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Key Points

- Because of its impact on quality of life and cognition, comorbid ADHD represents a key aspect of the management of children with epilepsy
- ADHD symptoms are not associated with the underlying epilepsy syndrome, the severity of epilepsy, and/or the ongoing antiepileptic drugs
- Methylphenidate resulted in a clinically significant decrease of ADHD symptoms in 75% of patients
- Response to methylphenidate was greater in girls but was not influenced by any epilepsy-related variables
- Methylphenidate was not associated with increased risk of seizure relapse
- Because of the limitations related to its observational design, the results of this study will have to be confirmed in a randomized double-blind controlled trial

Table 2. Effects of MPH on seizure control in children with epilepsy and ADHD: prospective studies

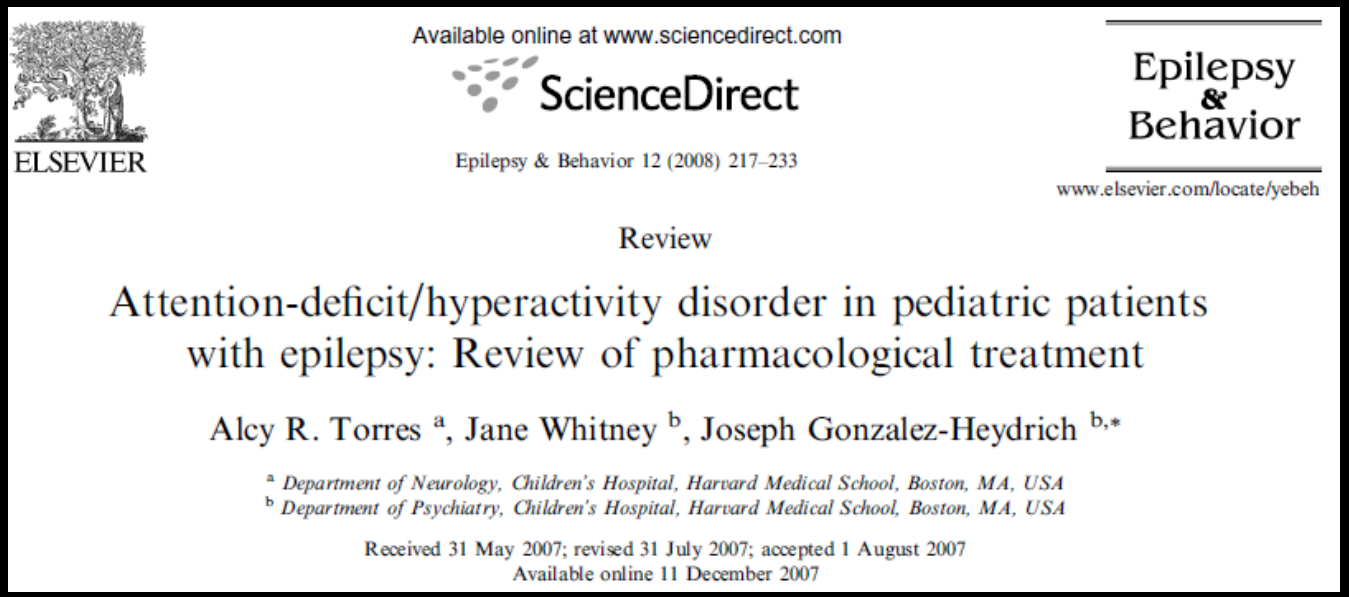
Study (first author, year)	N	Participants not having increase in seizure rate #	Participants not having increase in seizure rate %
Feldman, 1989	10	10	100
Gonzalez-Heydrich, 2010	33	33	100
Santos, 2013	22	18	82
Koneski, 2011	24	22	92
Yoo, 2009	25	23	92
Gucuyener, 2003	57	52	91
Gross-Tsur, 1997	30	27	90
Average	**201**	**185**	**92**

Table 3. Effects of MPH on ADHD symptoms in children with epilepsy and ADHD: prospective studies that provided raw data

Study (first author, year)	N	Participants improving from MPH use #	Participants improving from MPH use %
Feldman, 1989	10	7	70
Gross-Tsur, 1997	30	21	70
Santos, 2013	22	16	73
Koneski, 2011	24	17	71
Average	**86**	**61**	**71**

Ravi, 2016

CONCLUSION



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Review

Attention-deficit/hyperactivity disorder in pediatric patients with epilepsy: Review of pharmacological treatment

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In conclusion, although much research still needs to be done, the data on impairment from ADHD and the risks and benefits of its treatment argue that we should no more leave a child's ADHD untrated than leave his or her epilepsy untreataed