Data Related to Disease Similarity--A Case Study: PEACE Initiative in Pediatric Epilepsy

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PEDIATRIC EPILEPSY ACADEMIC CONSORTIUM FOR EXTRAPOLATION (PEACE)

- In disease states affecting both adults and children, drugs are often approved for adult use before development in children is completed or even started.
- Although antiepileptic drugs (AEDs) approved for use in adults can be prescribed off-label for children, this availability hampers pediatric drug development:
  - Raises parents' concerns about enrolling children with refractory epilepsy in a trial of a marketed drug with placebo.
  - Creates an operational disincentive to undertake the challenges of conducting double-blind, randomized, controlled efficacy trials in children with seizures.

PEACE

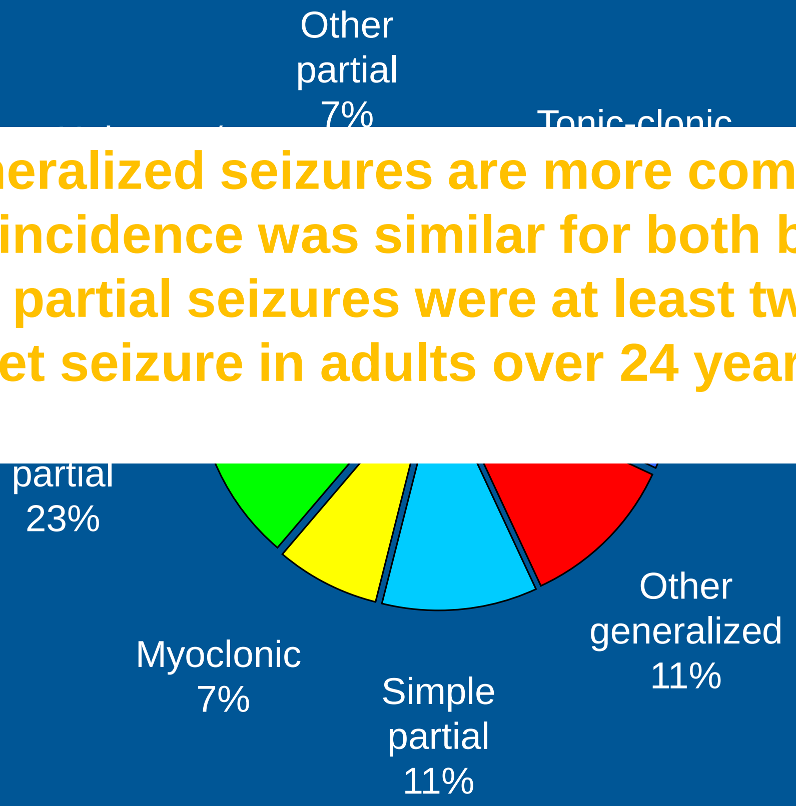
- In the absence of pediatric-specific labeling, prescribers lack critical information (e.g., dosing, tolerability/safety, age-specific monitoring) that can facilitate the appropriate and safe use of AEDs in this vulnerable population.
- Expediting pediatric access to new AEDs is compelling since epilepsy is the most common serious neurological disorder in children.
- Almost none of the AEDs approved for the management of focal (partial-onset) seizures included children <12 years of age in the initial clinical development program and were therefore marketed for use in older adolescents and adults.

PEACE

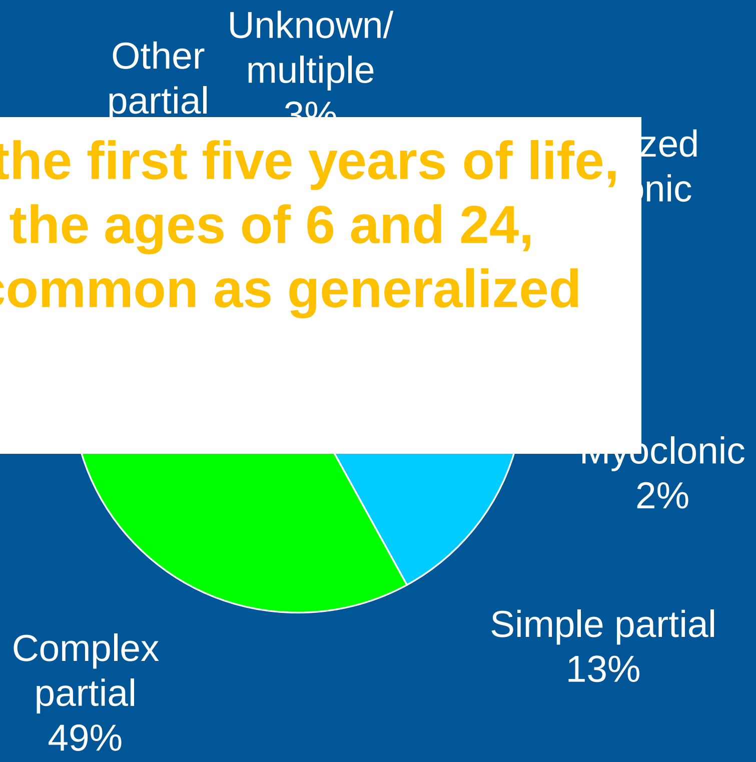
- Since focal seizures occur in both children and adults, efficacy data from adults can be successfully extrapolated to children if there is scientific consensus that disease progression and response to intervention are similar in adults and children.
- The focus of an argument for adult-to-pediatric efficacy data extrapolation in focal seizures is based on the similarity of seizure pathophysiology and the similarity of the clinical response to AEDs in terms of seizure control.

PREVALENCE OF GENERALIZED AND PARTIAL SEIZURES

Pediatric Patients <15 Years



Adults 35-64 Years



Generalized seizures are more common in the first five years of life, the incidence was similar for both between the ages of 6 and 24, and partial seizures were at least twice as common as generalized onset seizure in adults over 24 years.

Hauser, 1992

PEACE Rational

- Because anti-epileptic drugs are not evaluated as disease-modifying drugs (i.e. not anti-epileptogenic) the focus of an argument for adult-to-pediatric efficacy data extrapolation is based on the similarity of seizure pathophysiology.....
  - Key factors in E/I balance as function of age
  - Network maturation
  - Neurophysiological maturation
  - Seizure and EEG semiology
- and the similarity of the clinical response to AEDs in terms of seizure control.

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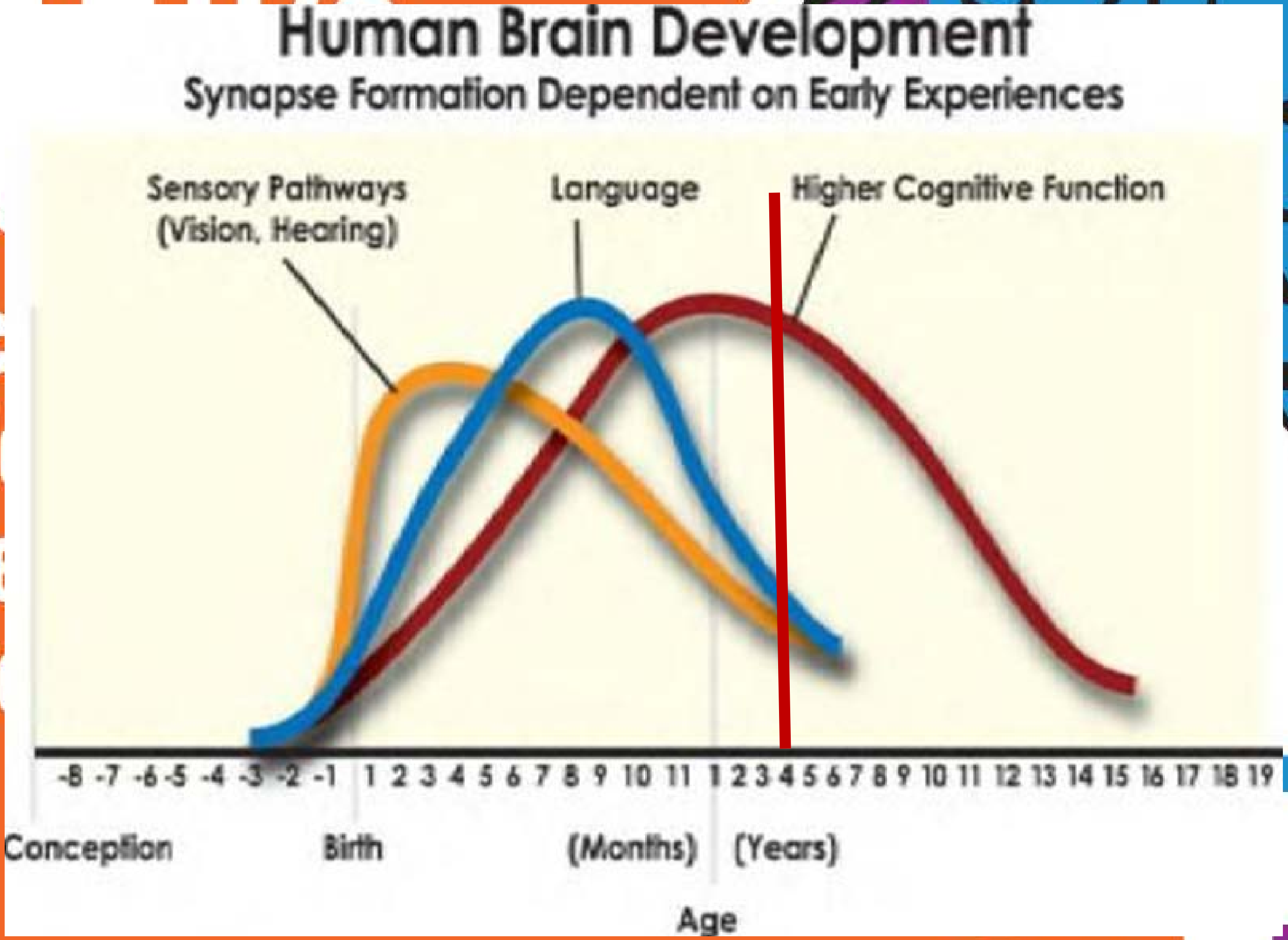
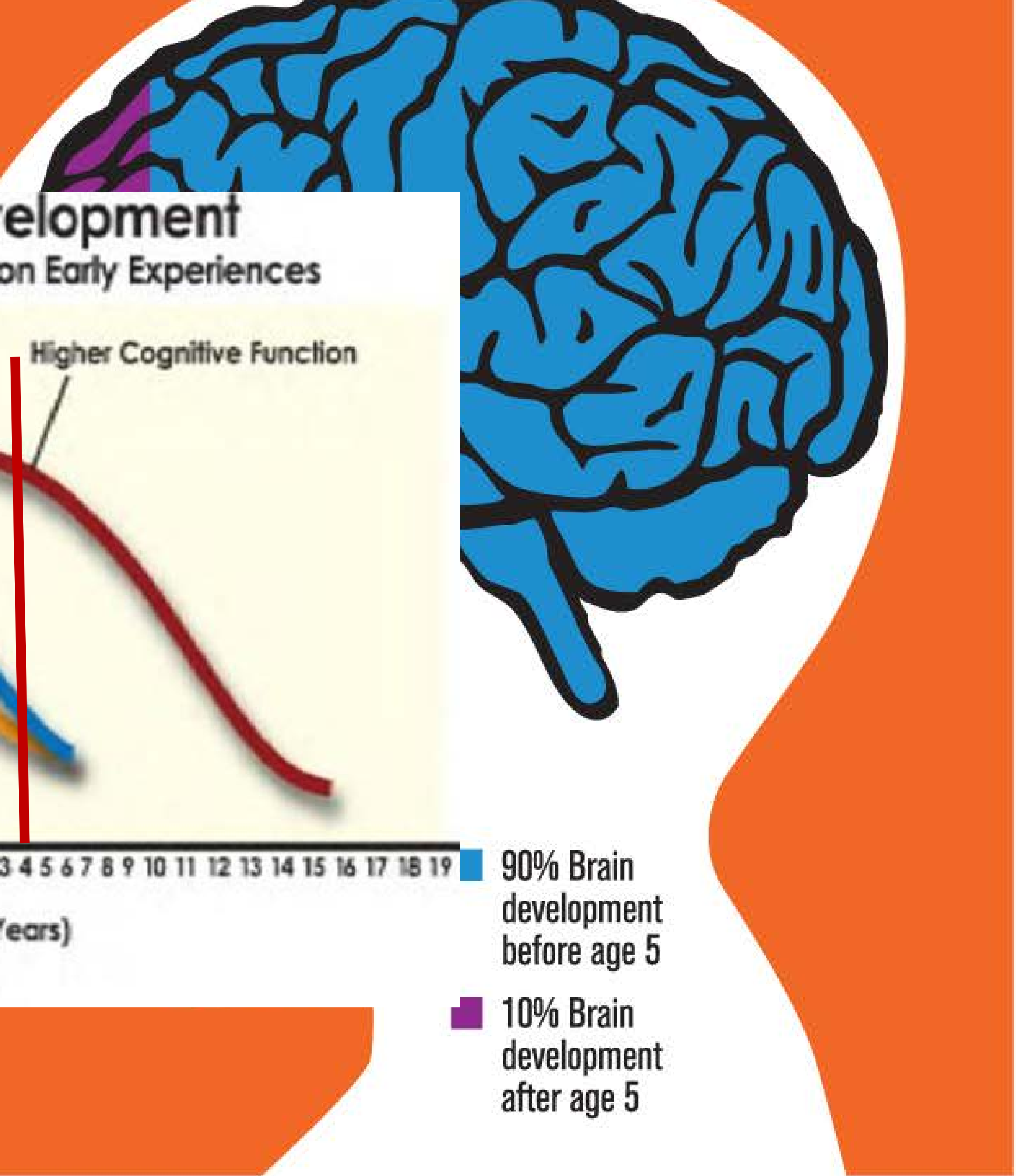
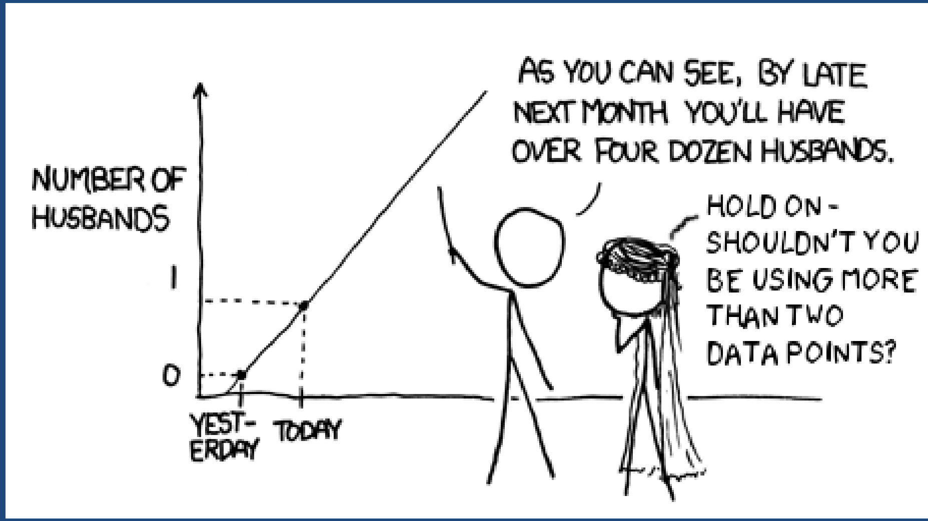
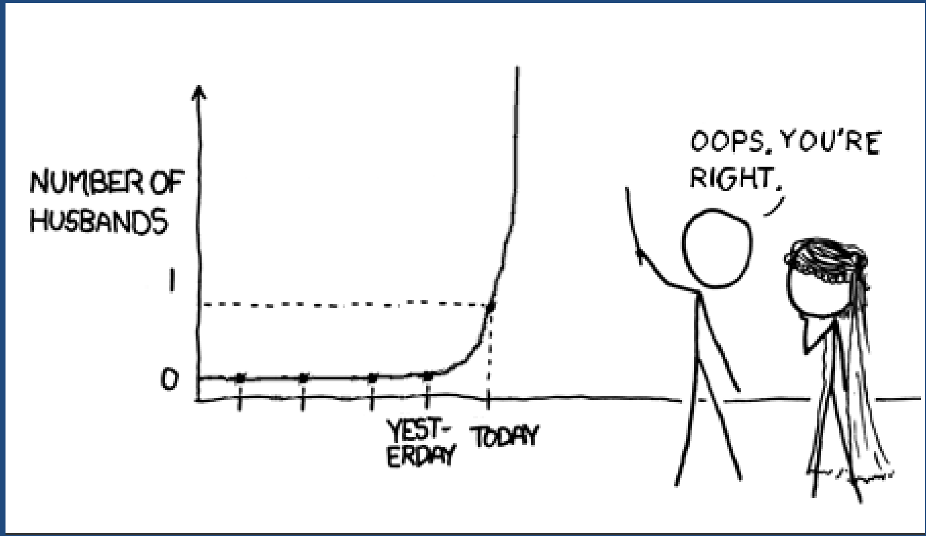


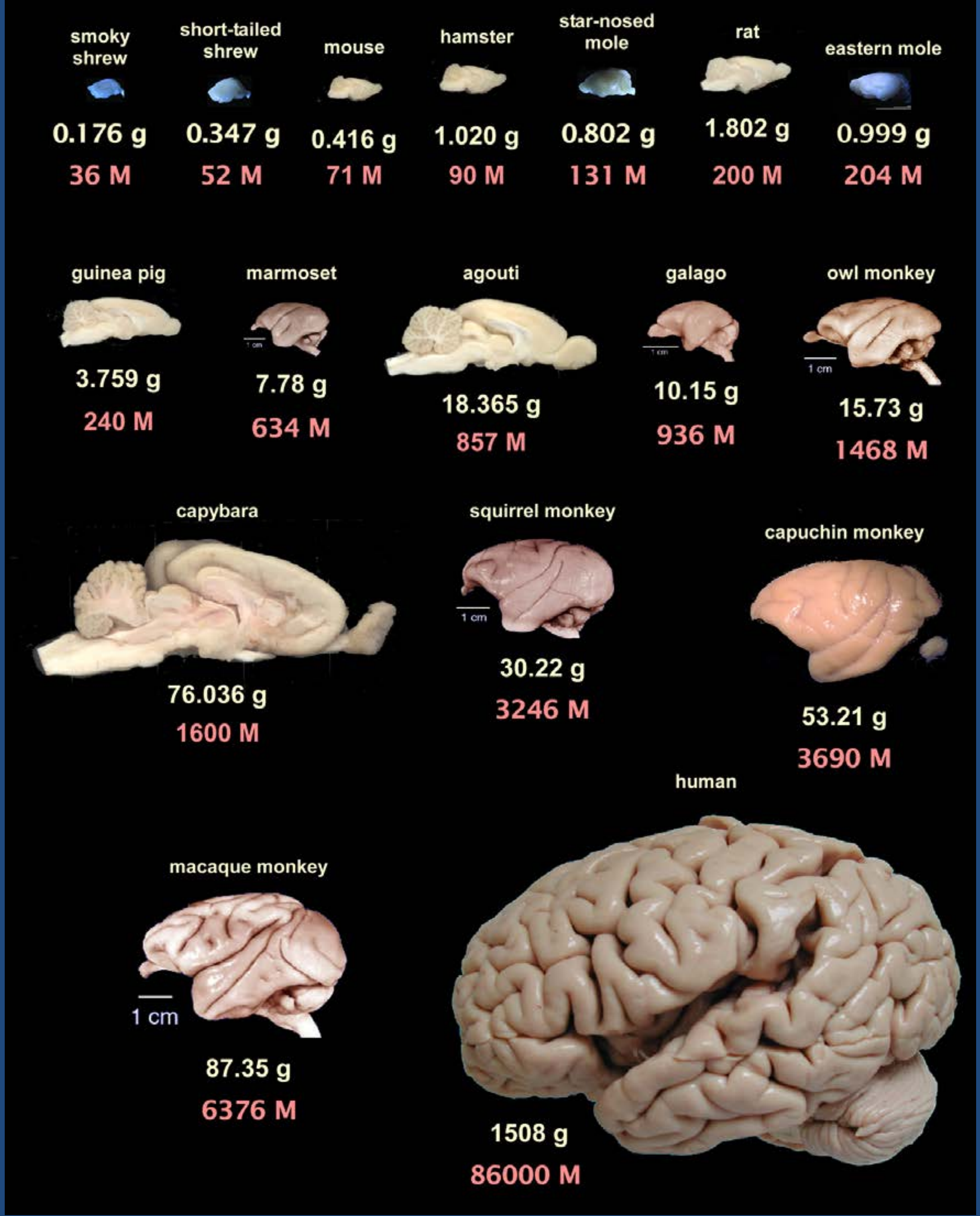


Source: Harvard Center for the Developing Child

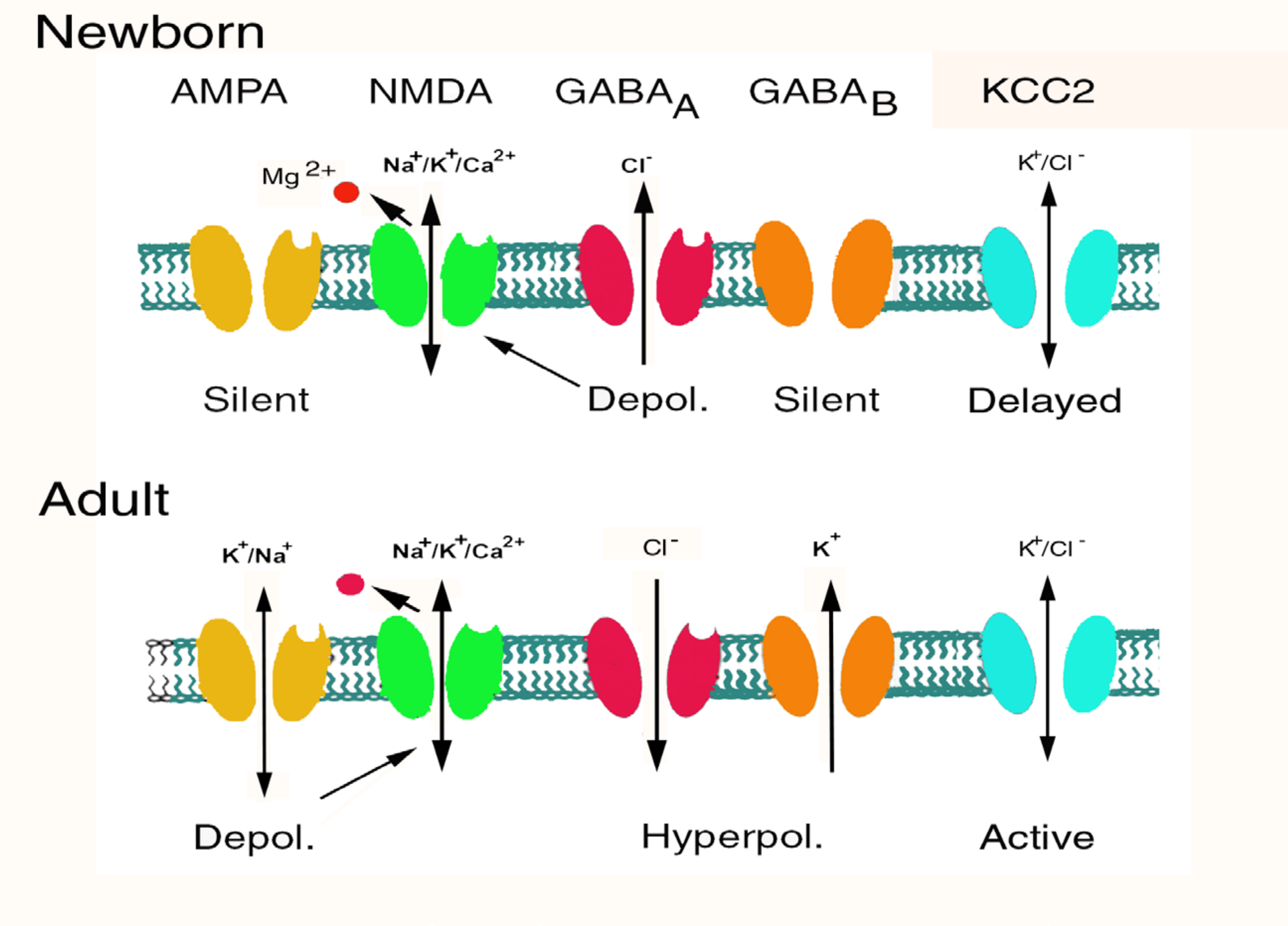
MY HOBBY: EXTRAPOLATING



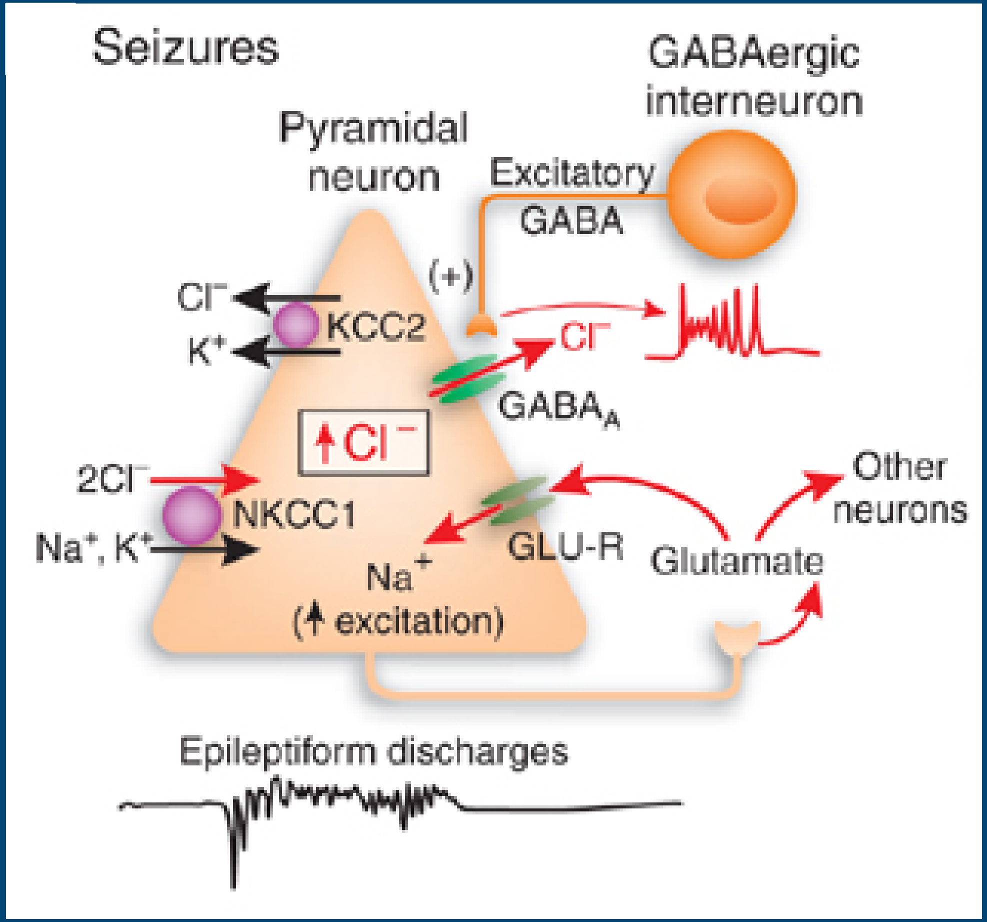




Developmental Aspects of Receptor Development

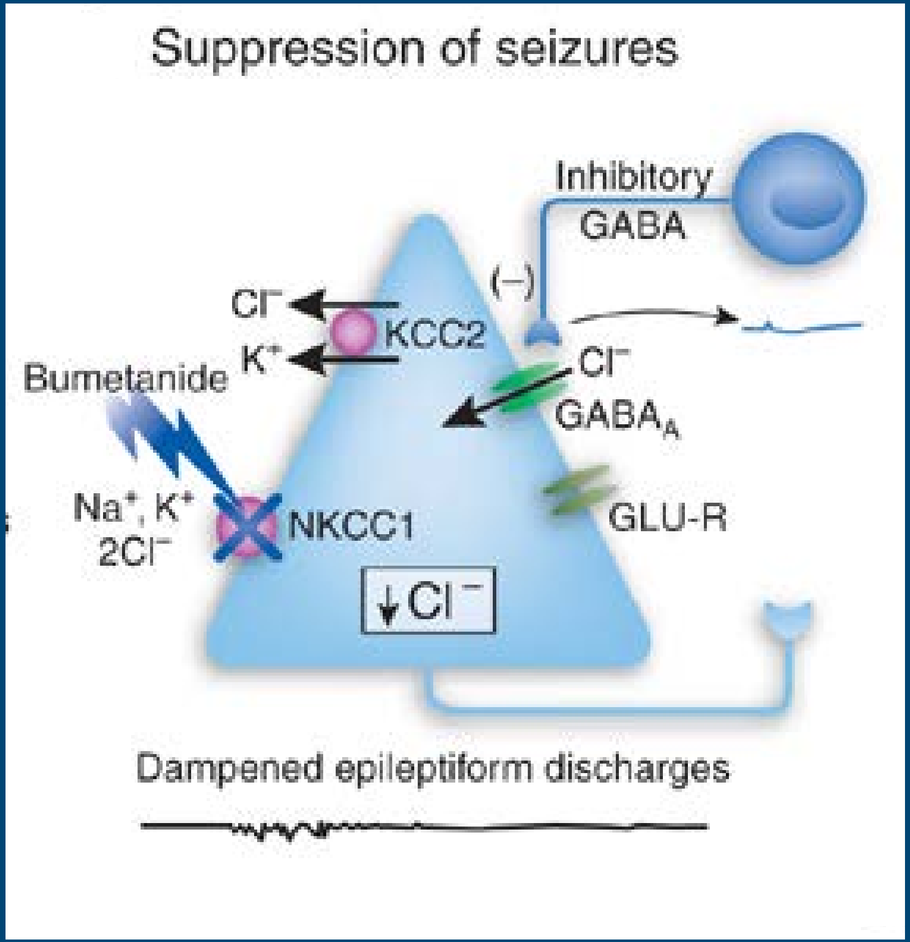


GABA is Excitatory in the Neonatal Brain

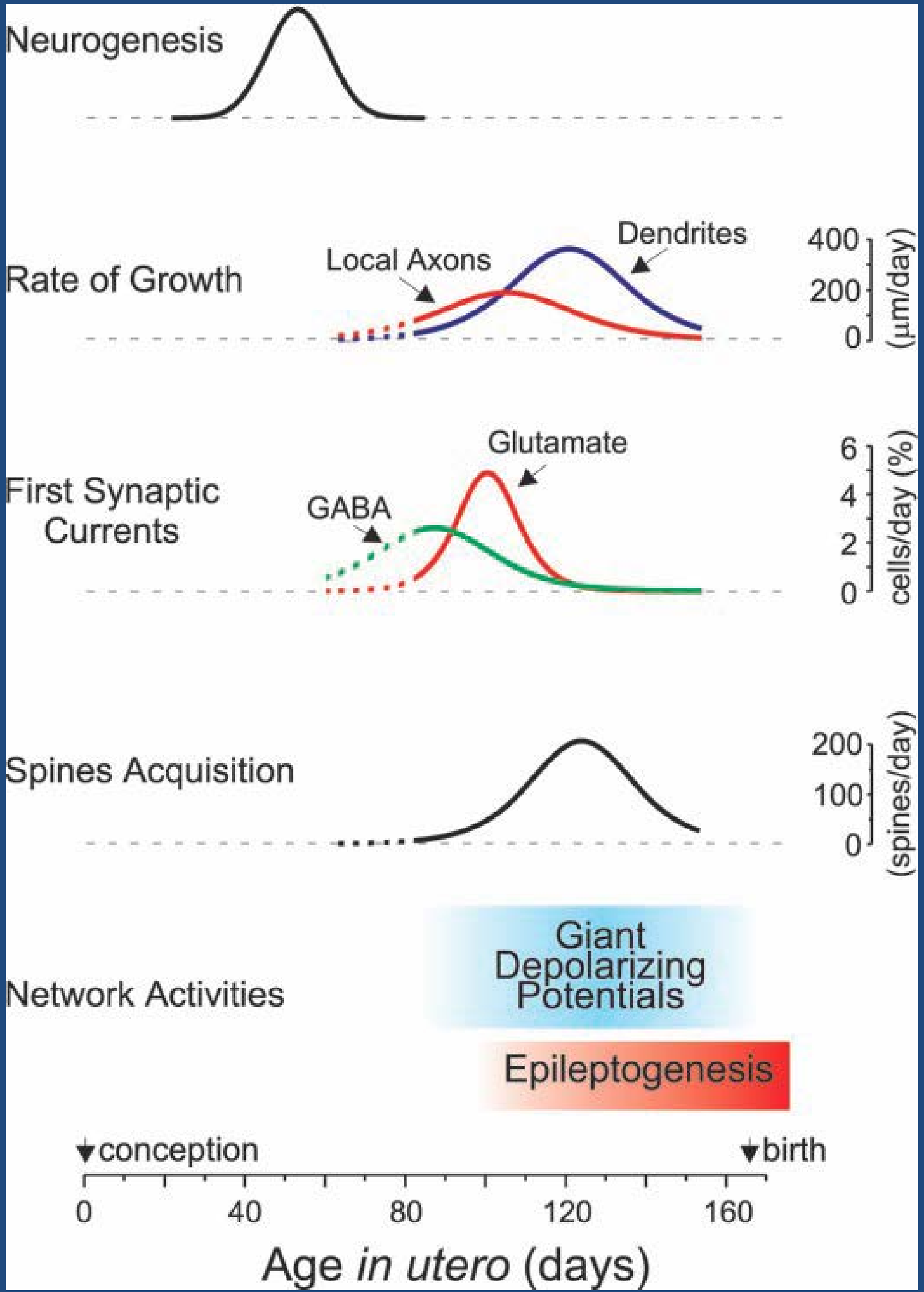


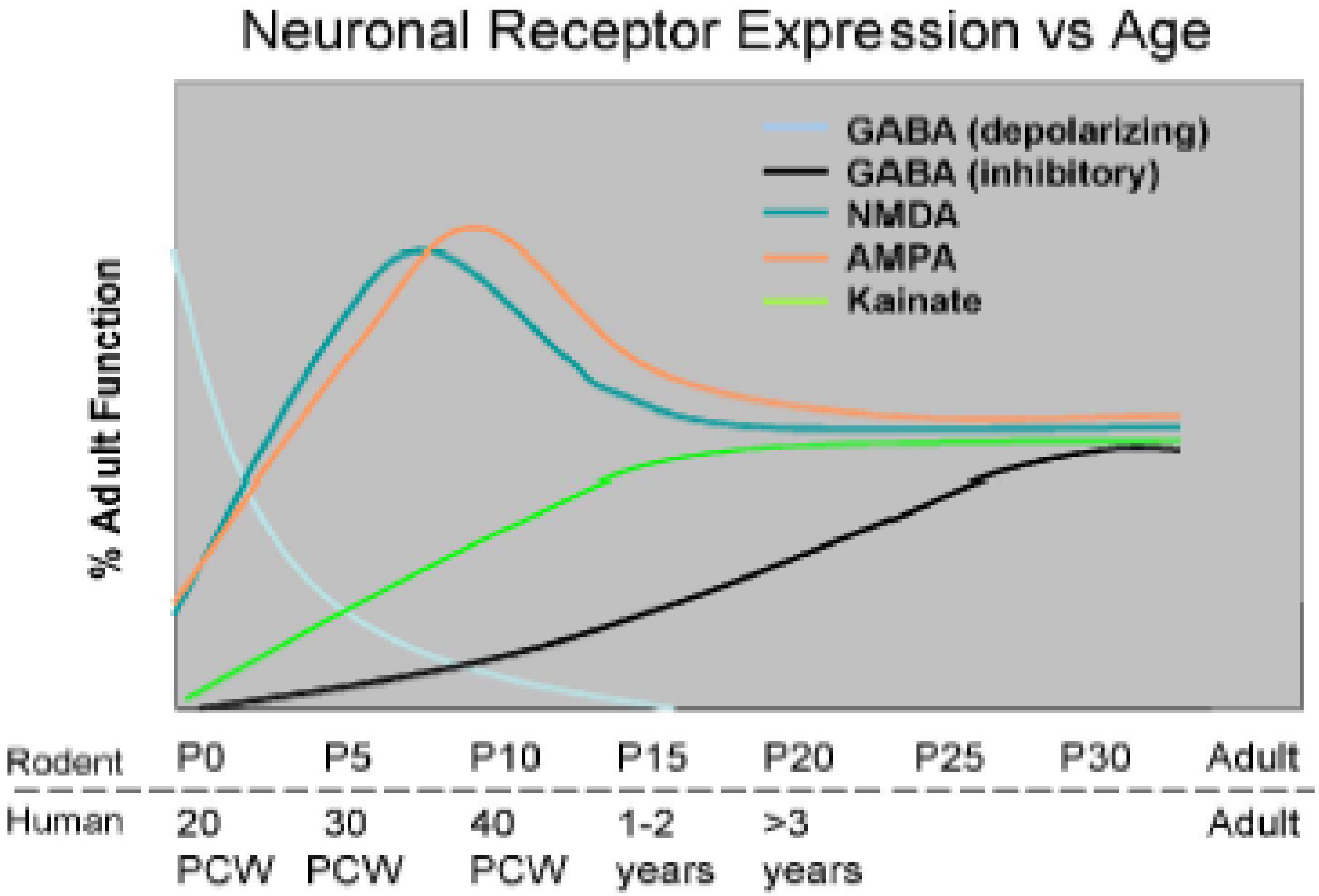
- Cl^- taken up by NKCC1
- Overwhelms Cl^- extrusion by KCC2
- High intracellular $[Cl^-]$
- +ve Cl^- equilibrium pot.
- $GABA_A$ activation results in Cl^- efflux & depolarization
- Depolarization causes glutamate release, further excitation via GLU-R

Bumetanide Potentiates the Effect of Phenobarbital



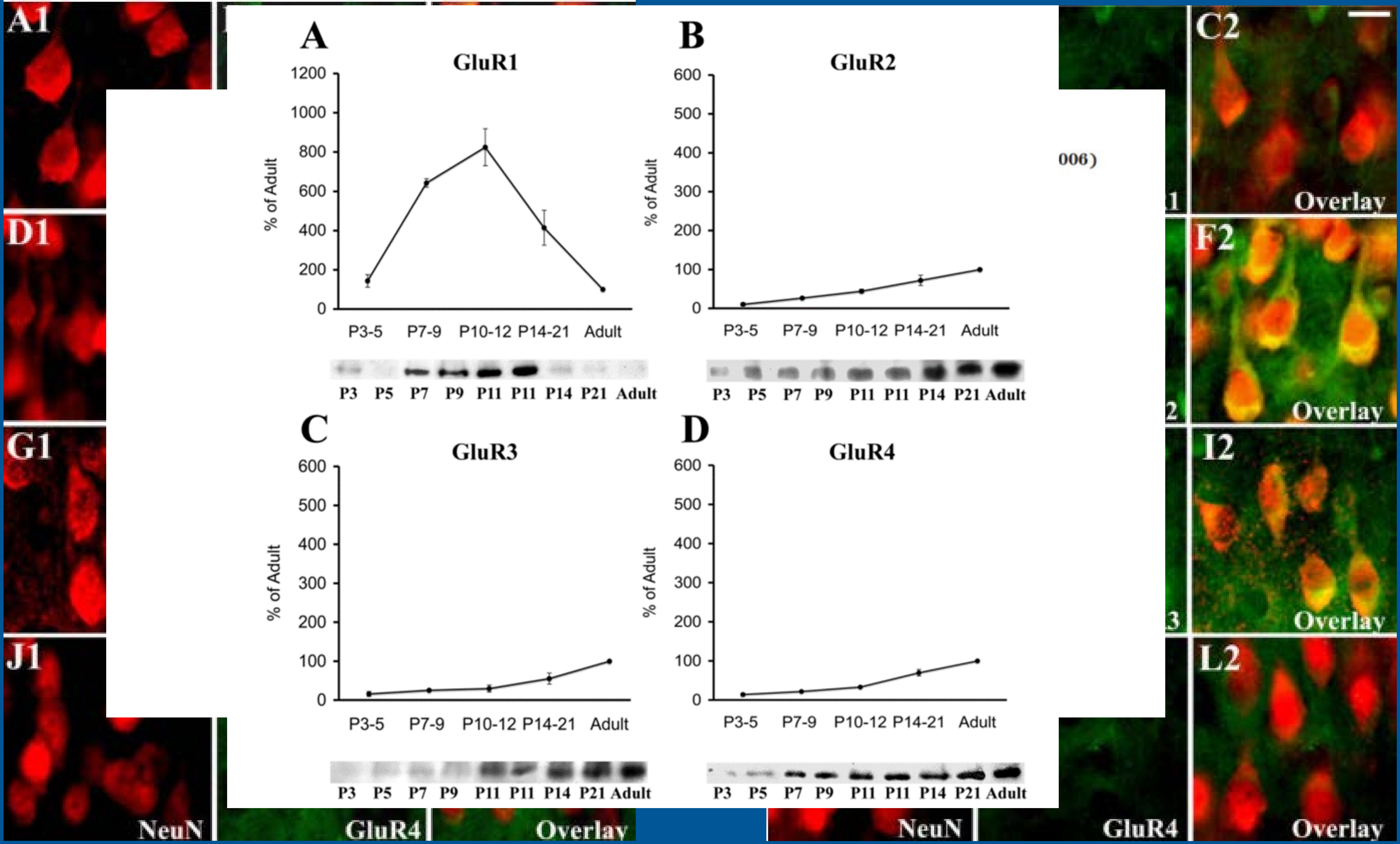
- Bumetanide selectively inhibits NKCC1
- Reduces intracellular [Cl^-]
- Reversal of Cl^- equilibrium potential
- $GABA_A$ activation causes Cl^- influx & hyperpolarization
- Hyperpolarization prevents excitation, glutamate release

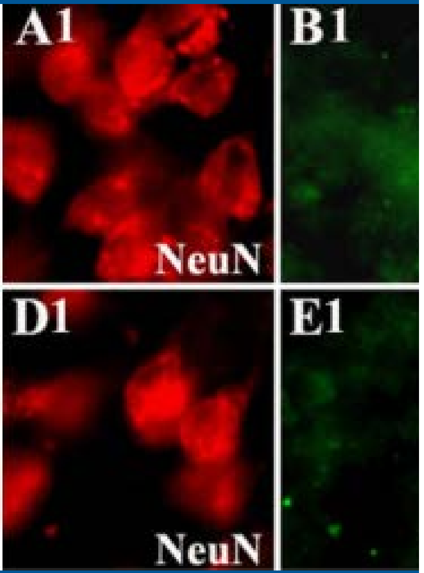

Neurogenesis
Rate of Growth
Local Axons
Dendrites
400
200
0
(μm/day)
First Synaptic Currents
GABA
Glutamate
6
4
2
0
cells/day (%)
Spines Acquisition
200
100
0
(spines/day)
Network Activities
Giant Depolarizing Potentials
Epileptogenesis
conception
birth
0
40
80
120
160
Age in utero (days)



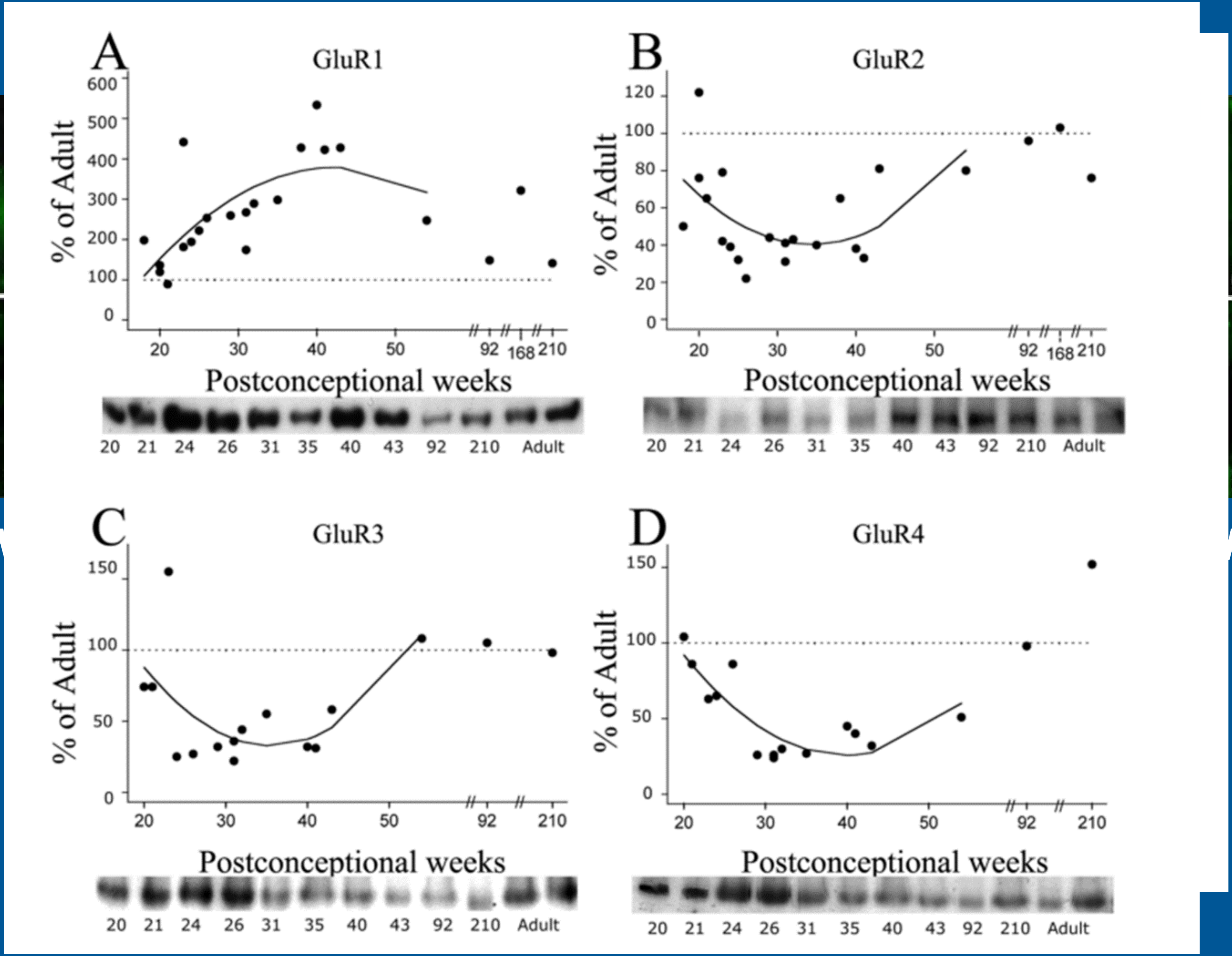
Jensen and Silverstein, 2007

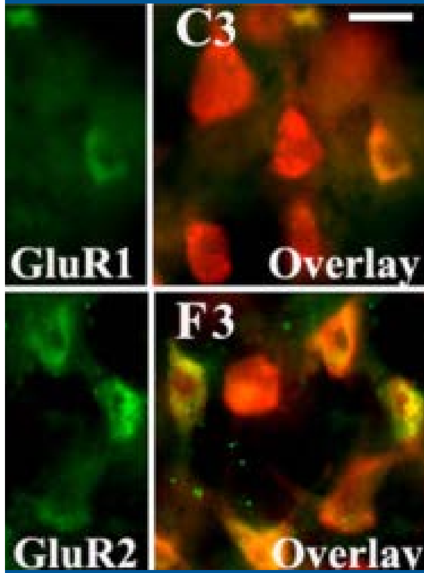
P11


A1
C2
Overlay
D1
F2
Overlay
G1
I2
Overlay
J1
L2
NeuN
GluR4
Overlay
NeuN
GluR4
Overlay
A
GluR1
% of Adult
0
200
400
600
800
1000
1200
P3-5 P7-9 P10-12 P14-21 Adult
P3 P5 P7 P9 P11 P11 P14 P21 Adult
B
GluR2
% of Adult
0
100
200
300
400
500
600
P3-5 P7-9 P10-12 P14-21 Adult
P3 P5 P7 P9 P11 P11 P14 P21 Adult
C
GluR3
% of Adult
0
100
200
300
400
500
600
P3-5 P7-9 P10-12 P14-21 Adult
P3 P5 P7 P9 P11 P11 P14 P21 Adult
D
GluR4
% of Adult
0
100
200
300
400
500
600
P3-5 P7-9 P10-12 P14-21 Adult
P3 P5 P7 P9 P11 P11 P14 P21 Adult


A1
NeuN
B1
D1
NeuN
E1

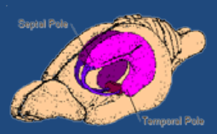
PCV


A
GluR1
% of Adult
600
500
400
300
200
100
0
20
30
40
50
92
168
210
Postconceptional weeks
20 21 24 26 31 35 40 43 92 210 Adult
B
GluR2
% of Adult
120
100
80
60
40
20
0
20
30
40
50
92
168
210
Postconceptional weeks
20 21 24 26 31 35 40 43 92 210 Adult
C
GluR3
% of Adult
150
100
50
0
20
30
40
50
92
210
Postconceptional weeks
20 21 24 26 31 35 40 43 92 210 Adult
D
GluR4
% of Adult
150
100
50
0
20
30
40
50
92
210
Postconceptional weeks
20 21 24 26 31 35 40 43 92 210 Adult

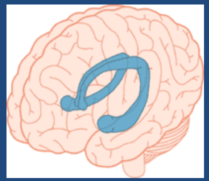

C3
GluR1
Overlay
F3
GluR2
Overlay

/ 168

Theta Rhythm

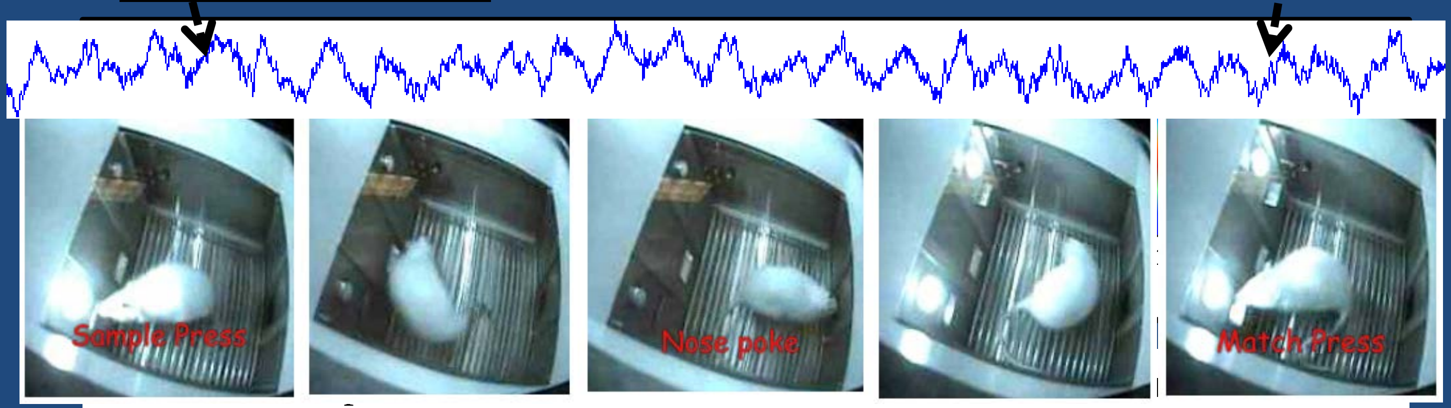


Rats: 4-12Hz



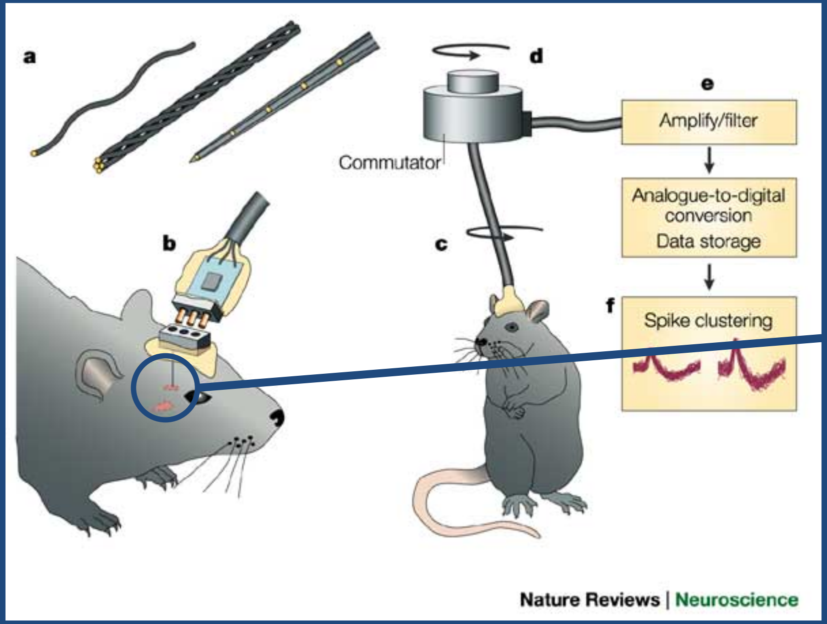
Humans: 4-8Hz

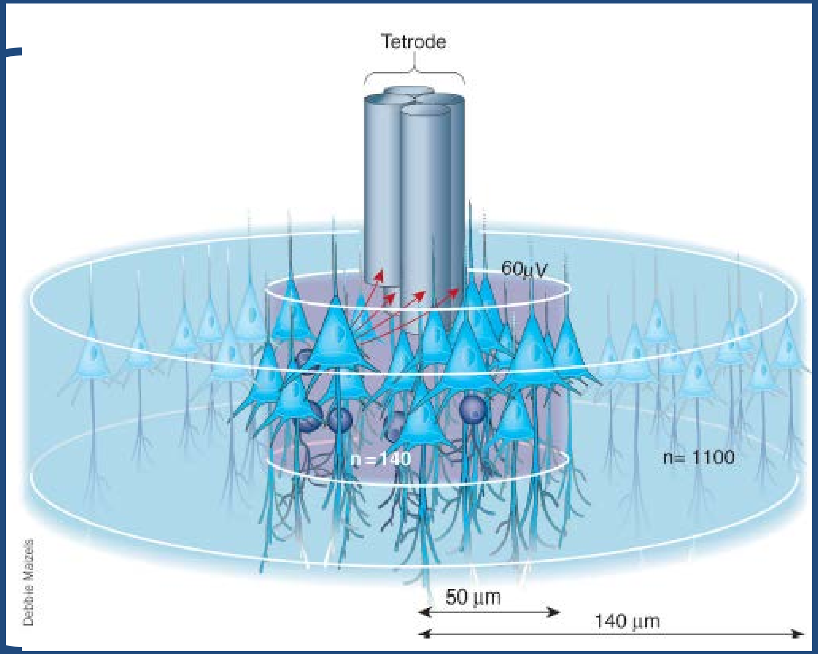
1 second



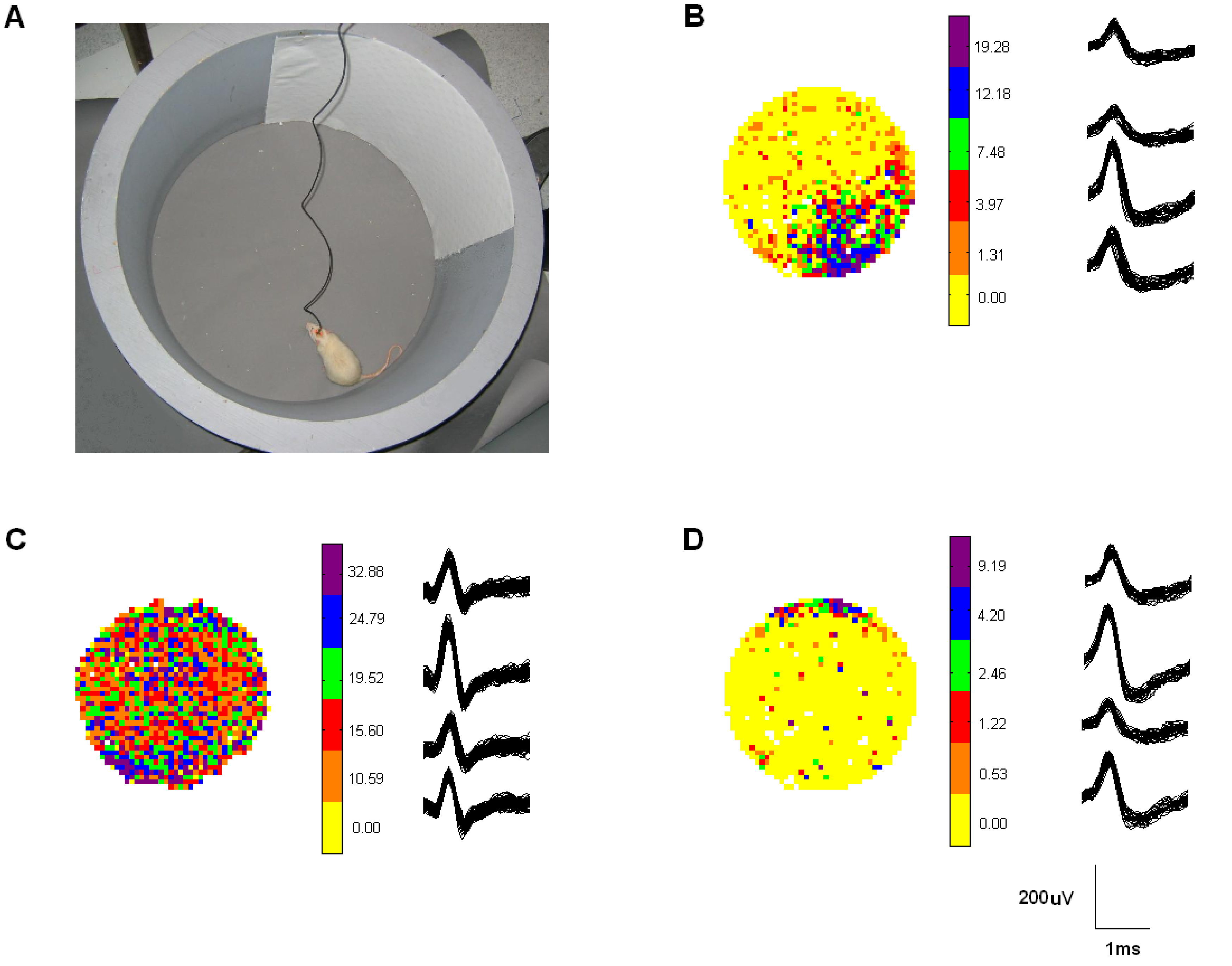
Time-locked to lever pressing behavior (Sample & Match presses)

Single Unit Recording Method

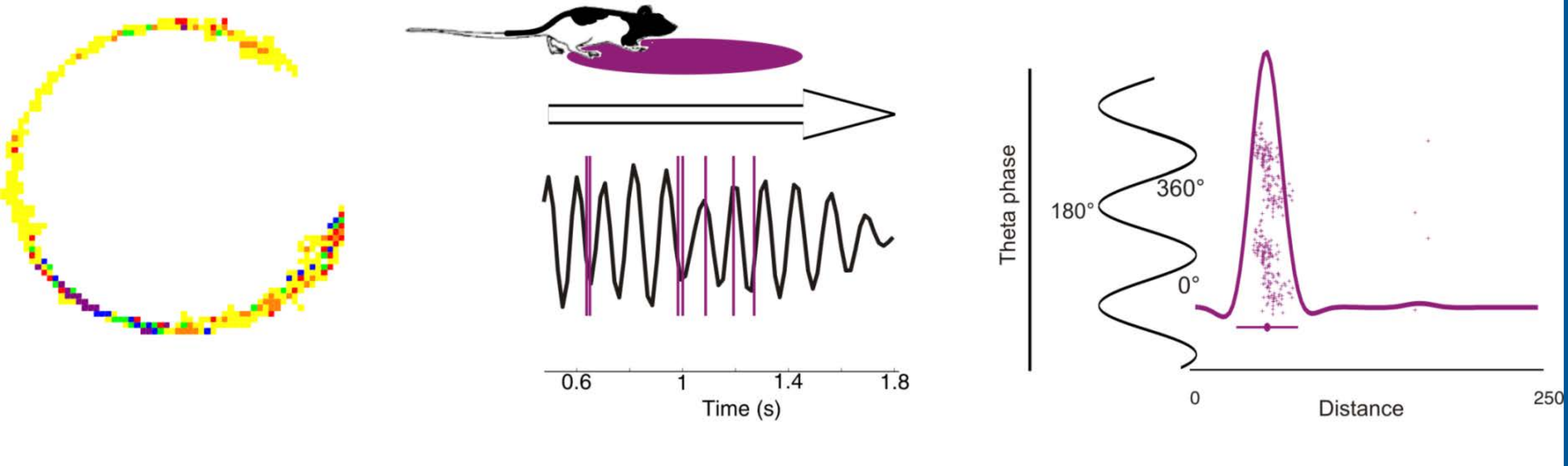




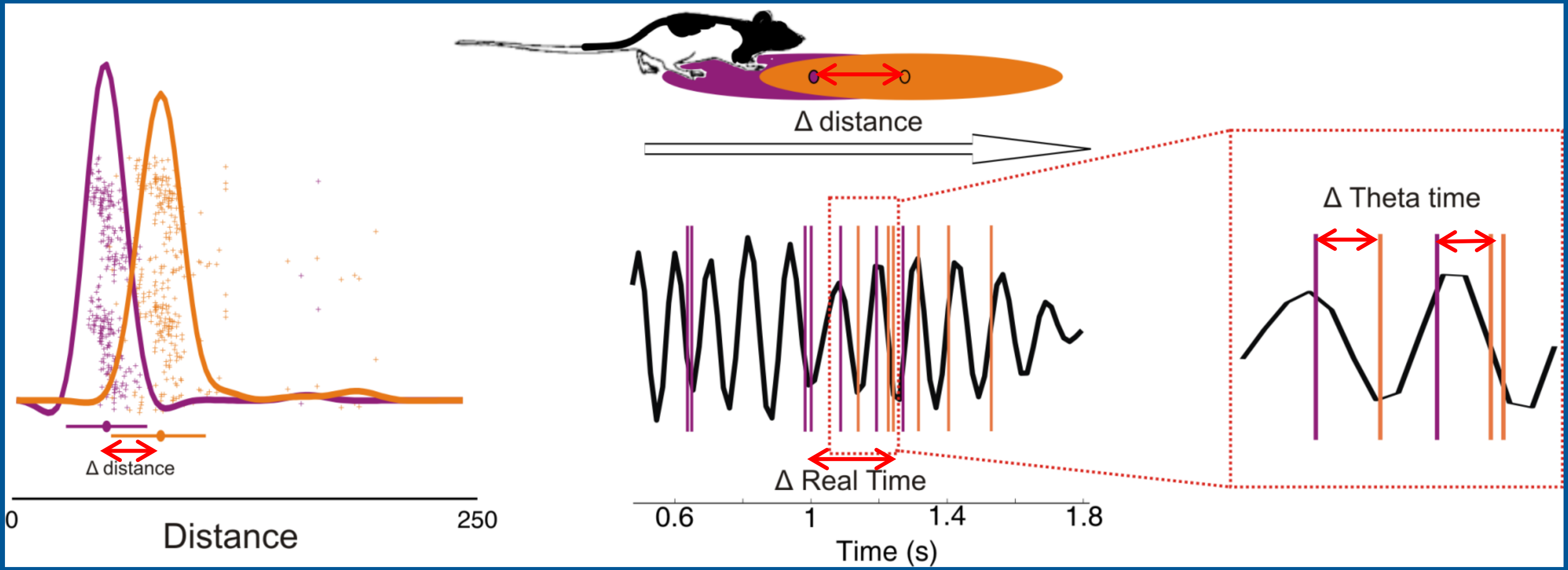
Buzsáki, *Nature Neuroscience*, 2004


A
B
19.28
12.18
7.48
3.97
1.31
0.00
C
32.88
24.79
19.52
15.60
10.59
0.00
D
9.19
4.20
2.46
1.22
0.53
0.00
200uV
1ms

Rate Coding

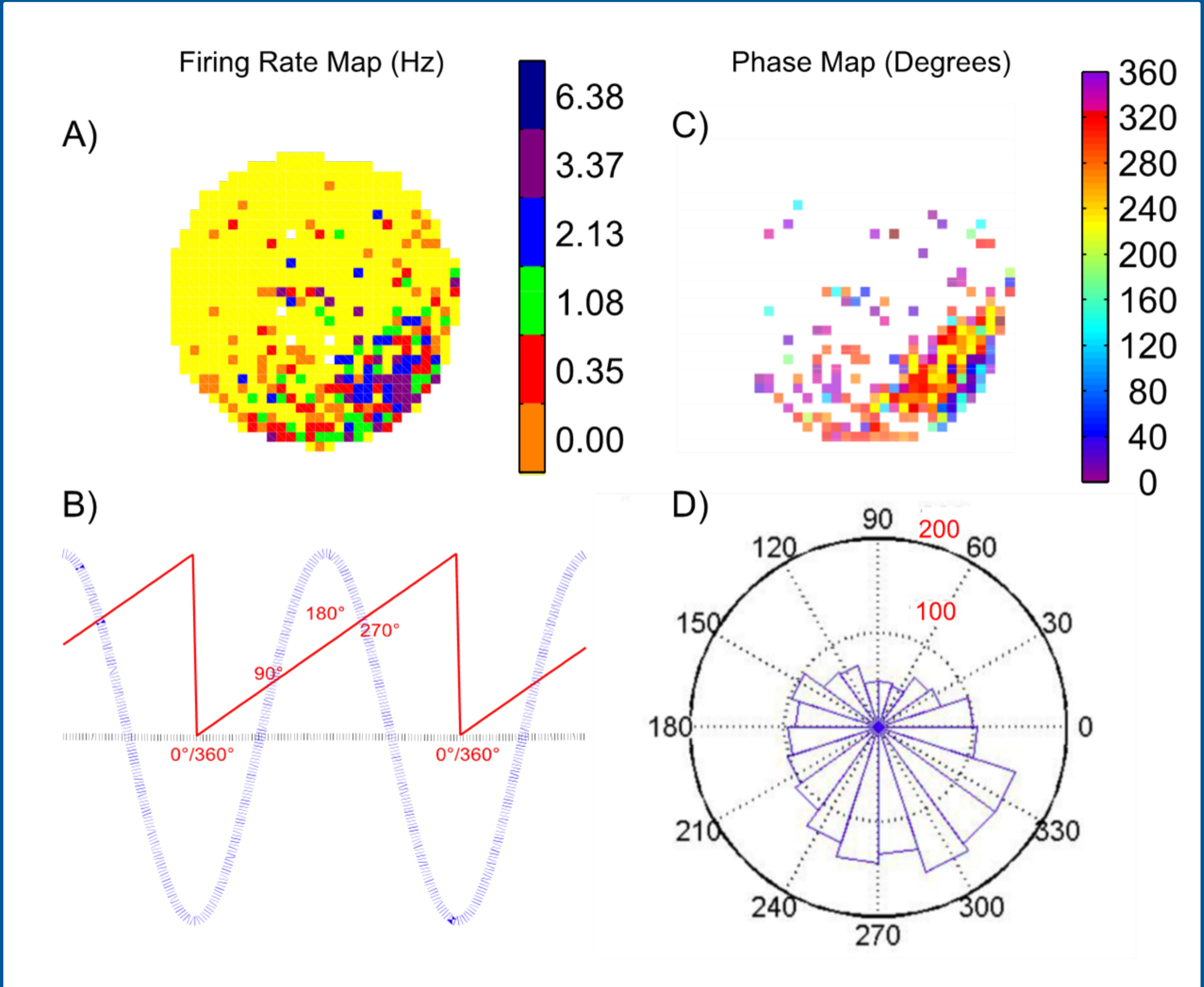


0.6
1
1.4
1.8
Time (s)
Theta phase
180°
360°
0°
0
Distance
250

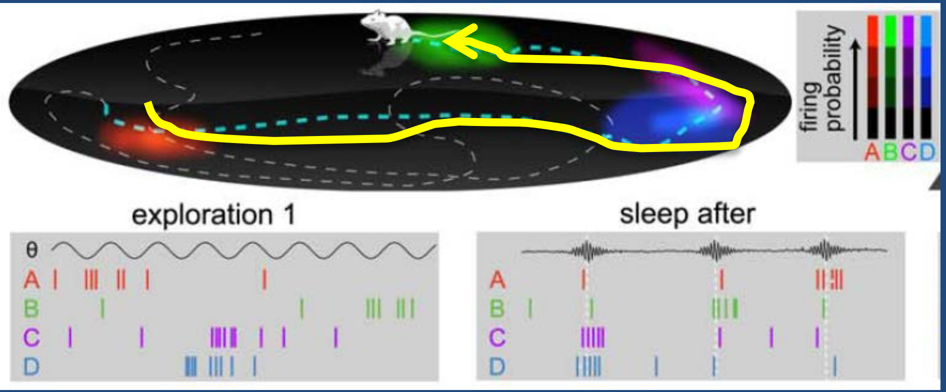


Δ distance
Δ distance
0
Distance
250
Δ Real Time
0.6
1
1.4
1.8
Time (s)
Δ Theta time

Beyond Rate Coding – Temporal Coding of AP's by the Phase of Theta

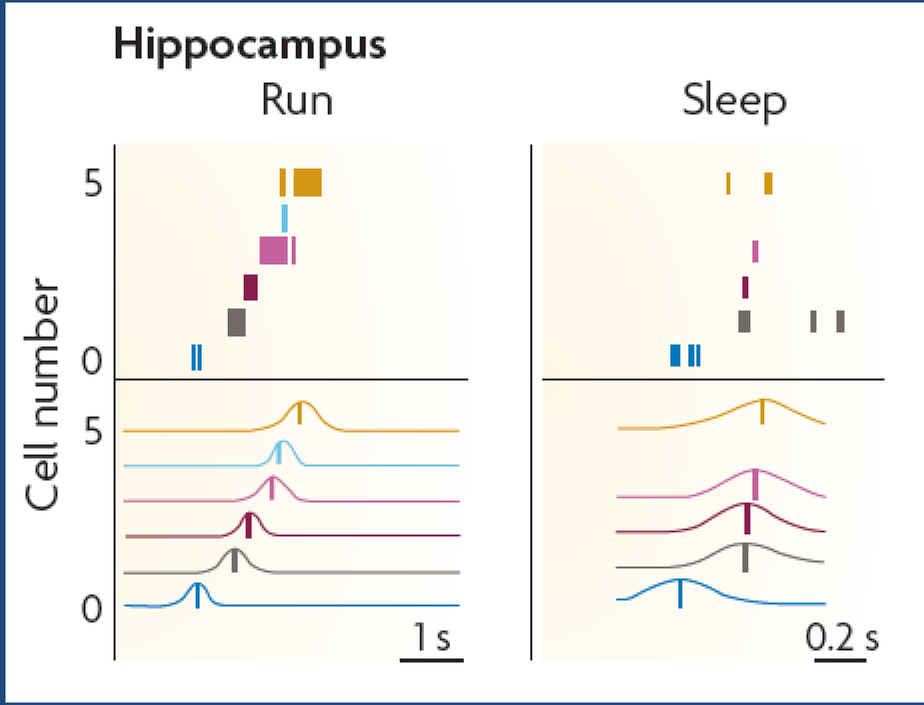


Replay of Place Cells in Sleep



O'Neill, Trends in Neurosciences, 2010

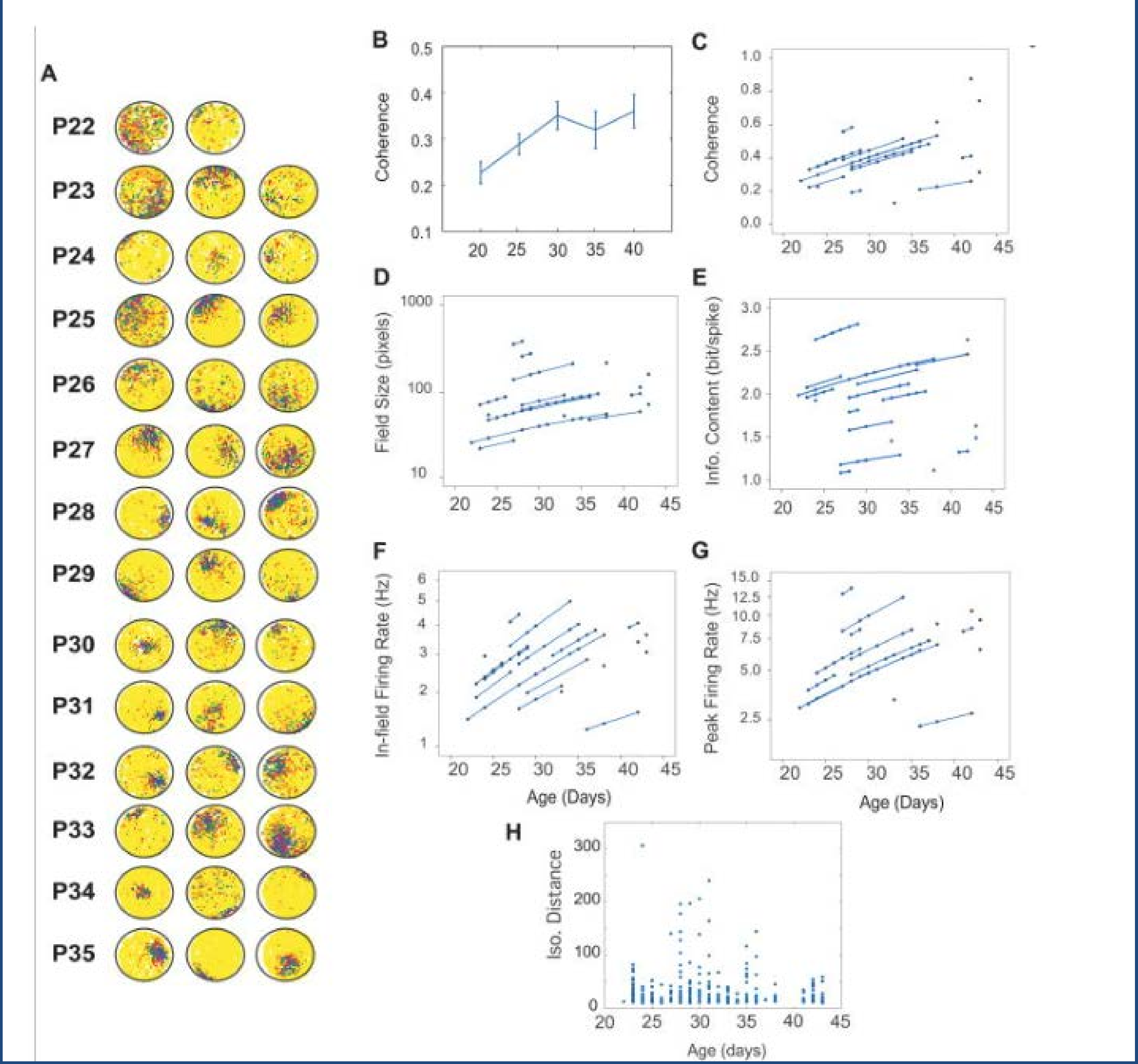
Matt Wilson



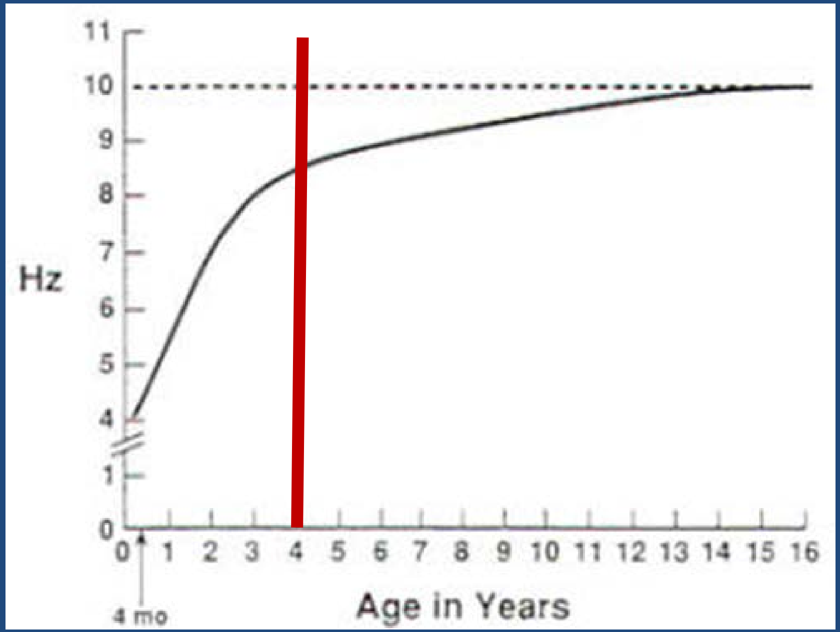
Diekelmann and Born, Nature Neuroscience Reviews, 2010
modified from Ji and Wilson, Nature Neuroscience, 2007

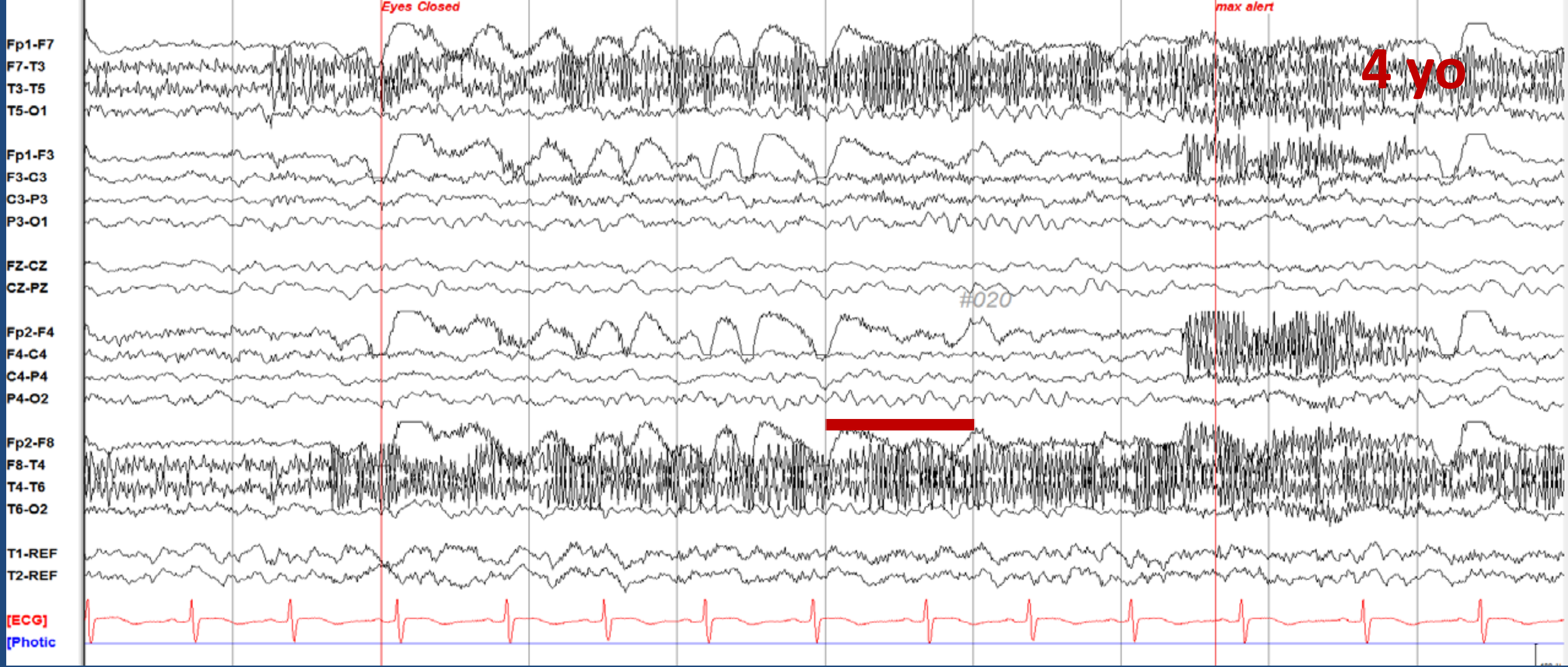
Maturational Dynamics of Place Cells in Immature Rats

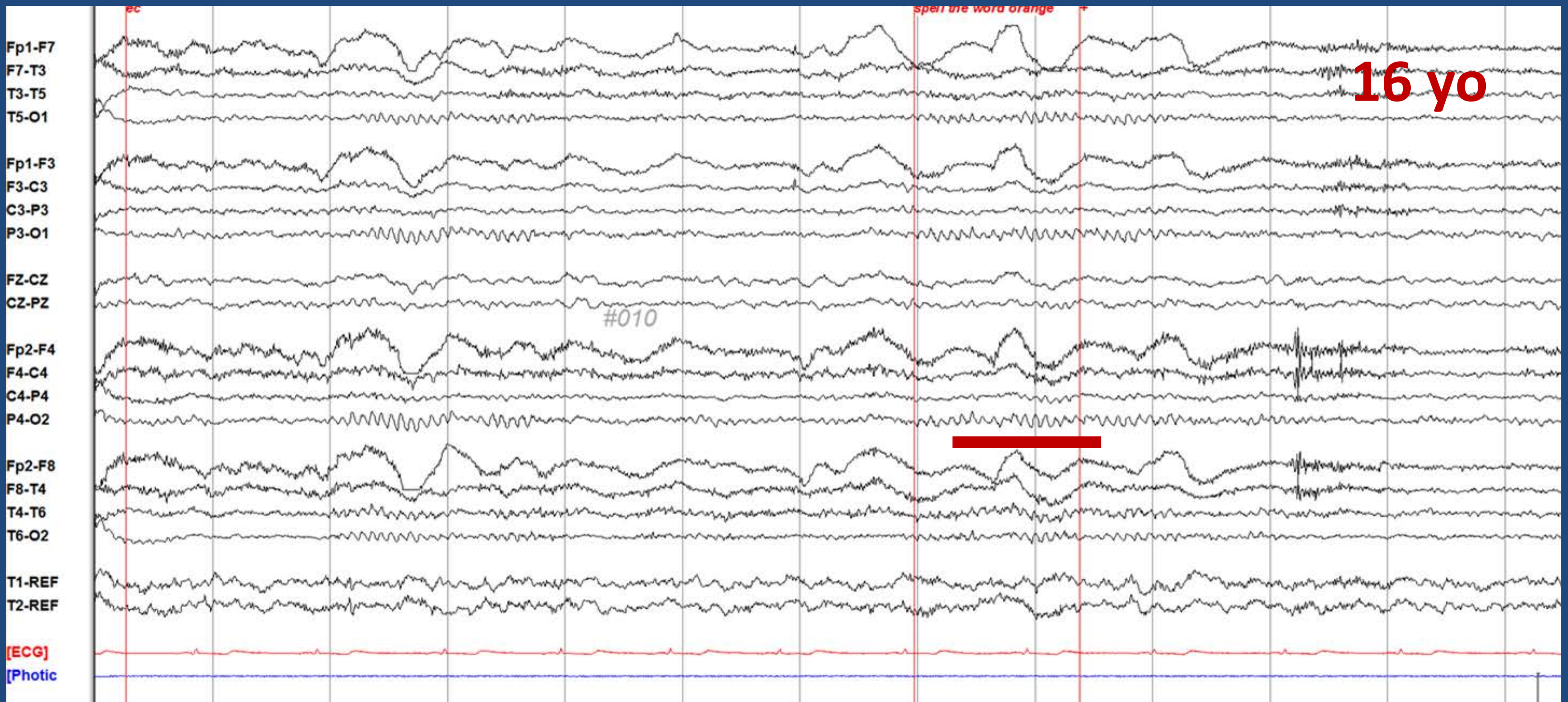
- Ontogeny of the place cell system in rats studied between P22 and P43, a time during which there was a rapid improvement in spatial behavior.
- Place cells with adult like firing fields were observed at the earliest ages, but were few in number.
- Firing rate and stability increased with age and the average spatial signal of all pyramidal cells improved.

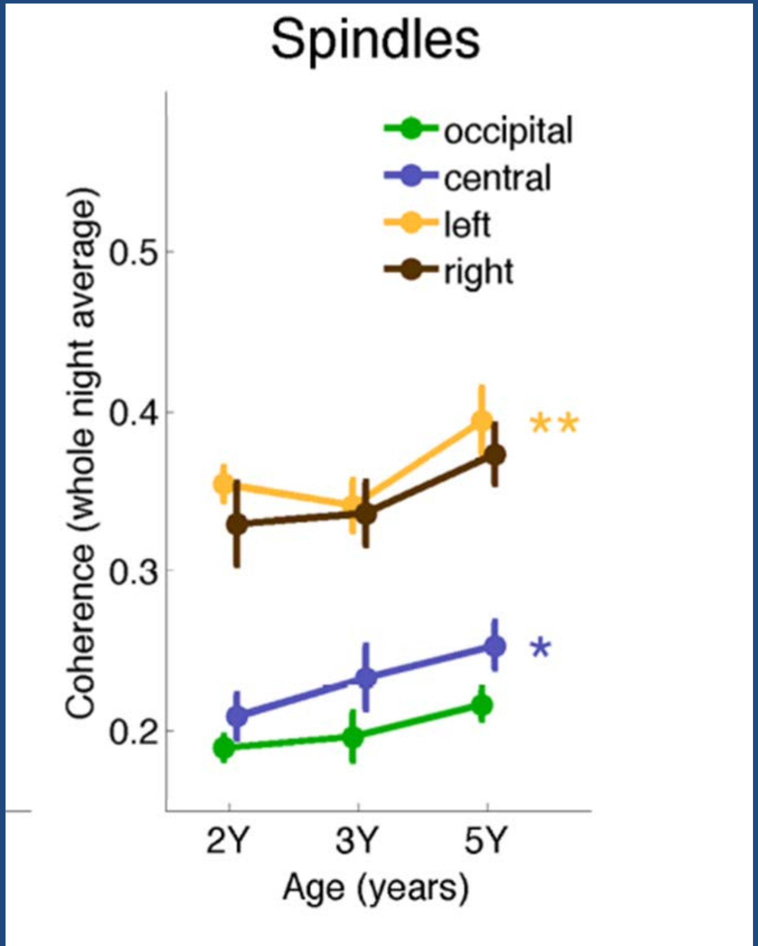


Alpha Frequency

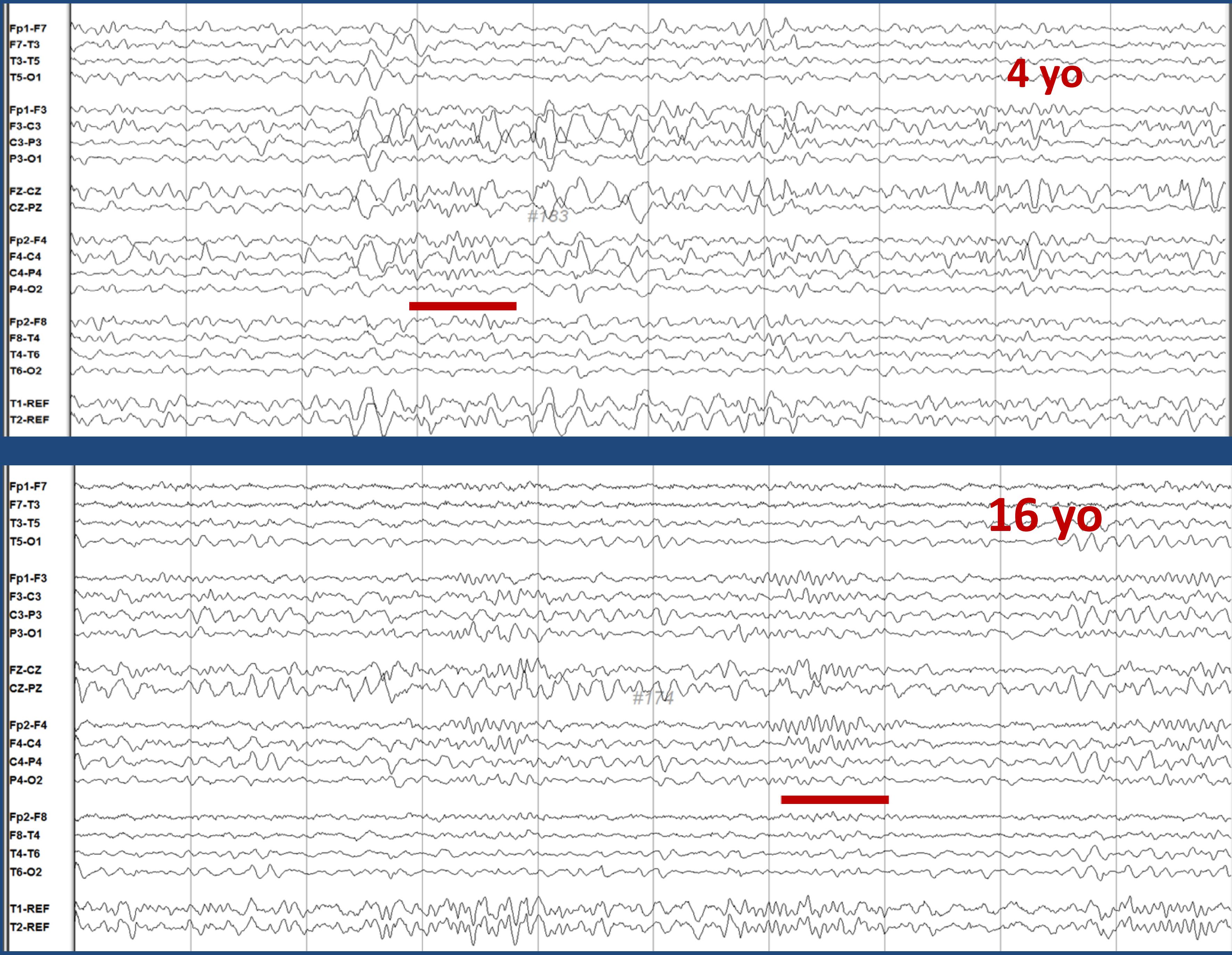








Kurth et al., 2013



Epilepsia, **42**(8):986–990, 2001
Blackwell Science, Inc.

The Ontogeny of Partial Seizures in Infants and Young Children

*Douglas R. Nordli, Jr., *Maxine M. Kuroda, and †Lawrence J. Hirsch

**Epilepsy Center, Children's Memorial Hospital, Chicago, Illinois; and †Comprehensive Epilepsy Center, Columbia University, New York–Presbyterian Hospital, New York, New York, U.S.A.*

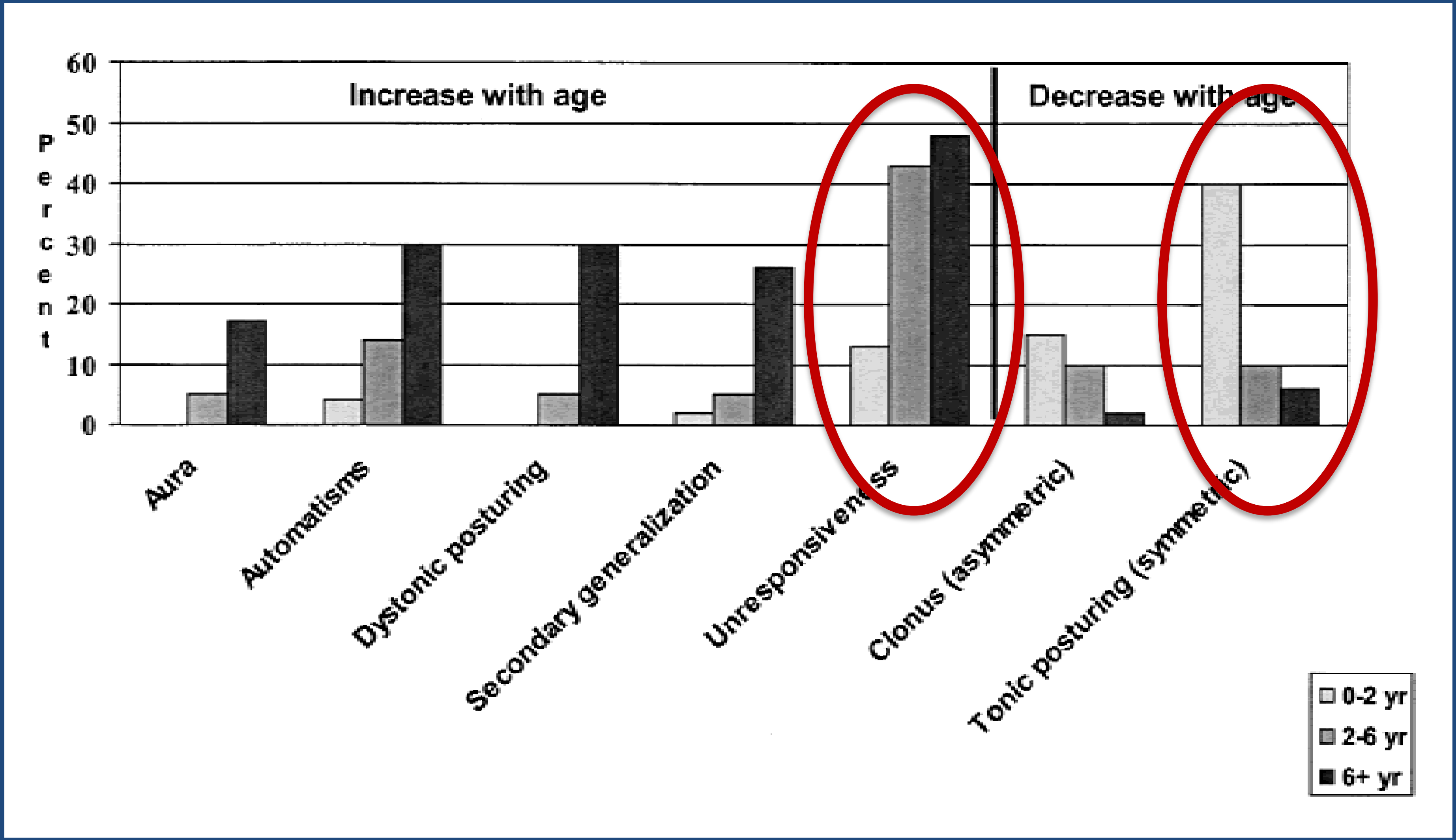
Summary: *Purpose:* To describe the clinical manifestations of partial seizures in the pediatric population as a function of age.

Methods: Using the database of the pediatric epilepsy monitoring unit (Children's Hospital of New York), clinical and EEG characteristics of partial seizures were distributed by age groups 0–2, 2–6, and 6+ years for 123 patients who had at least one such seizure with a clear EEG correlate during their admission. χ^2 tests for trend were used to examine clinical and EEG features as a function of age.

Results: The frequency of aura, limb automatisms, dystonic posturing, secondary generalization, and unresponsiveness increased with age, whereas asymmetric clonus and symmetric tonic posturing decreased with age. There were no clear changes in the types of EEG ictal patterns observed with age; however, partial seizures emanating from the anterior regions of the brain tended to increase with age, whereas those from the posterior regions tended to decrease with age.

Conclusions: Important differences exist in the clinical expression of seizures between young children and adults. These findings will contribute to a better understanding of ictal ontogeny that will promote more accurate classification of seizures and of the epilepsies in young patients. Such efforts can be used to identify young patients for focal epilepsy surgery and to select appropriate anticonvulsive medications. **Key Words:** Epilepsy—Seizures—Infants—Age-related features.

Seizure Characteristics that Change with Age



Nordli et al., 2001

EEG Parameters by Age

Parameter	Age (yr) and number 0–2 (48)	2–6 (21)	6+ (54)	Total (123)	χ^2_{trend}
Location					
Frontal	8 (17)	5 (24)	14 (26)	27 (22)	1.3
Anterior temporal	4 (8)	3 (14)	8 (15)	15 (12)	1.0
Rolandic	8 (17)	2 (10)	3 (6)	13 (11)	3.3
Occipital	10 (21)	1 (5)	1 (2)	12 (10)	10.8[a]
Temporoparietal	14 (29)	5 (24)	10 (19)	29 (24)	1.6
Hemispheric	3 (6)	3 (14)	8 (15)	14 (13)	1.8
Vertex	0	0	4 (7)	4 (3)	2.7
Feature					
Isolated spike	1 (2)	0	1 (2)	2 (2)	0
Rhythmic delta	14 (29)	4 (19)	12 (22)	30 (24)	0.6
Rhythmic theta/alpha	25 (52)	15 (71)	27 (50)	67 (55)	0.1
Run (sharps/spikes)	7 (15)	3 (14)	5 (9)	15 (12)	0.7
Attenuation	1 (2)	0	1 (2)	2 (2)	0
Low-voltage fast	5 (10)	0	9 (17)	14 (13)	1.0
Irregular slowing	1 (2)	0	0	1 (1)	0.2

Nordli et al., 2001

Efficacy of antiepileptic drugs in adults predicts efficacy in children

A systematic review

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ABSTRACT

Objective: Due to the challenges inherent in performing clinical trials in children, a systematic review of published clinical trials was performed to determine whether the efficacy of antiepileptic drugs (AEDs) in adults can be used to predict the efficacy of AEDs in the pediatric population.

Methods: Medline/PubMed, EMBASE, and Cochrane library searches (1970–January 2010) were conducted for clinical trials of partial-onset seizures (POS) and primary generalized tonic-clonic seizures (PGTCS) in adults and in children <2 and 2–18 years. Independent epidemiologists used standardized search and study evaluation criteria to select eligible trials. Forest plots were used to investigate the relative strength of placebo-subtracted effect measures.

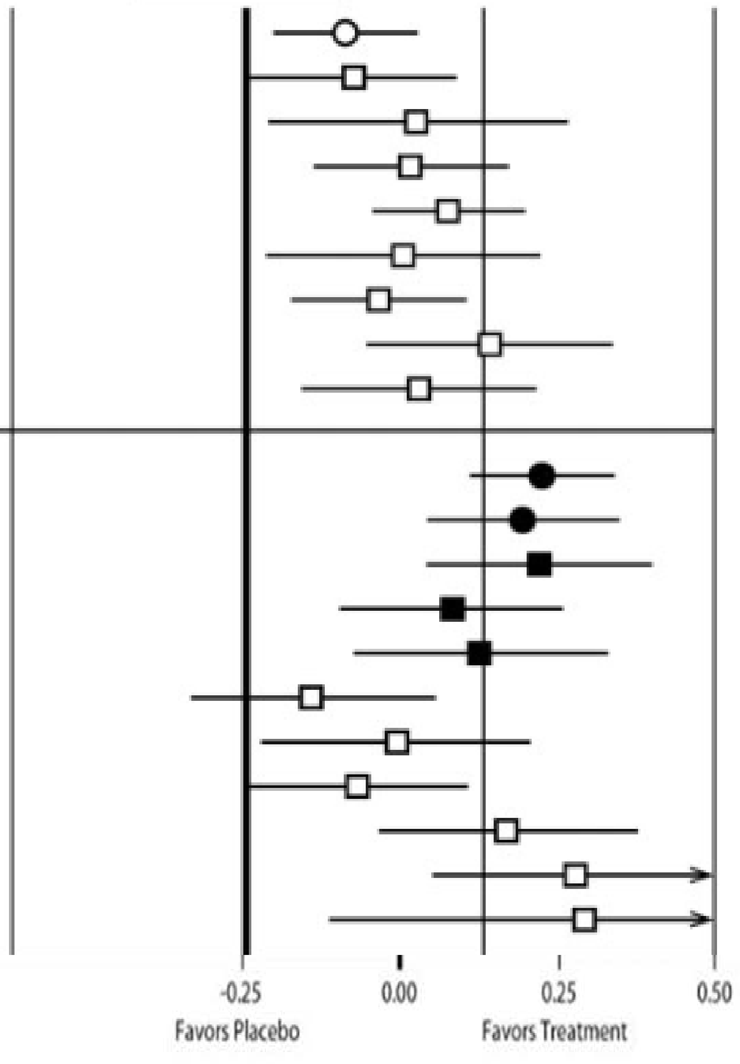
Results: Among 30 adjunctive therapy POS trials in adults and children (2–18 years) that met evaluation criteria, effect measures were consistent between adults and children for gabapentin, lamotrigine, levetiracetam, oxcarbazepine, and topiramate. Placebo-subtracted median percent seizure reduction between baseline and treatment periods (ranging from 7.0% to 58.6% in adults and from 10.5% to 31.2% in children) was significant for 40/46 and 6/6 of the treatment groups studied. The ≥50% responder rate (ranging from 2.0% to 43.0% in adults and from 3.0% to 26.0% in children) was significant for 37/43 and 5/8 treatment groups. In children <2 years, an insufficient number of trials were eligible for analysis.

Conclusions: This systematic review supports the extrapolation of efficacy results in adults to predict a similar adjunctive treatment response in 2- to 18-year-old children with POS.
Neurology® 2012;79:1482–1489

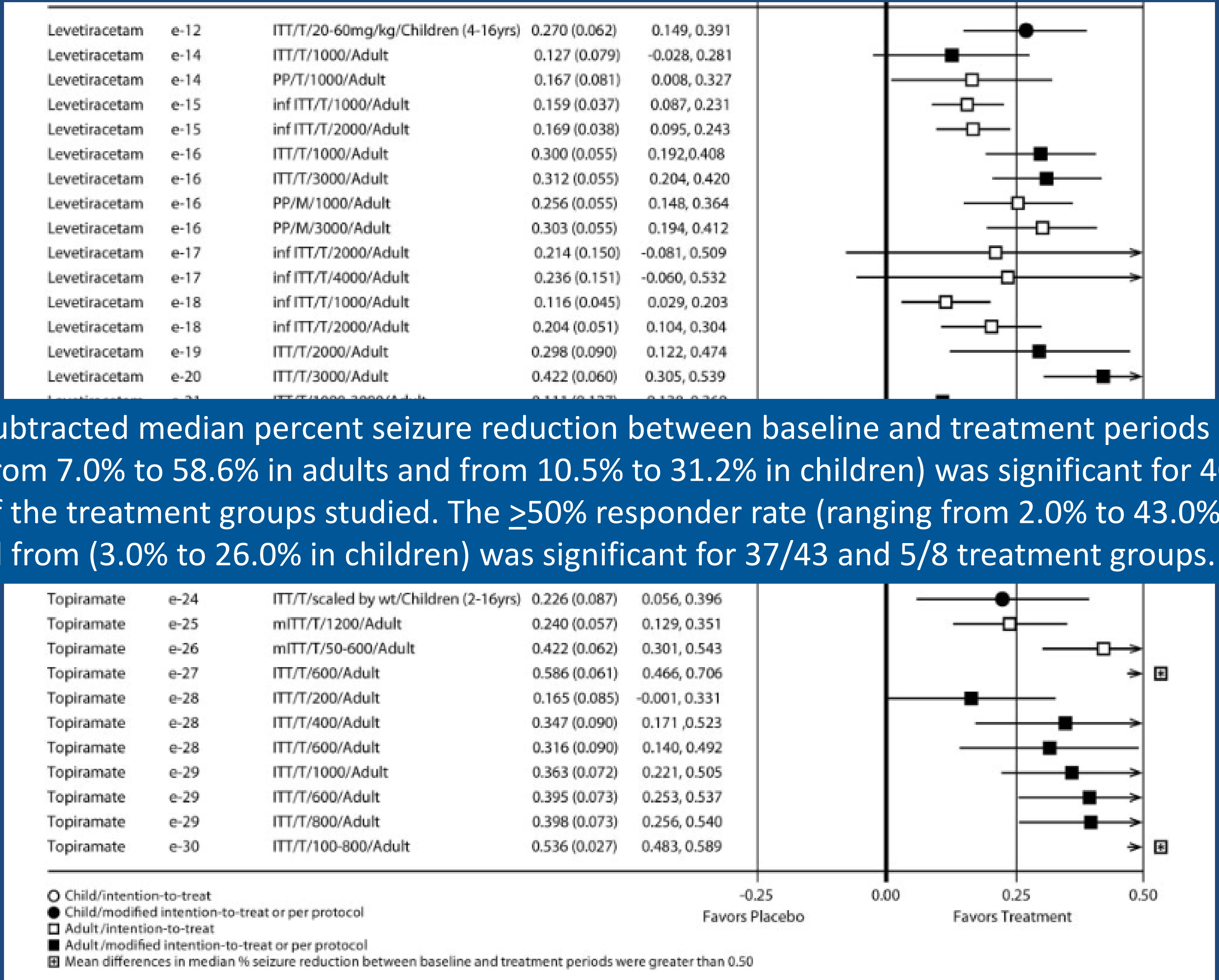
Efficacy Comparison of Differences in Median % Seizure Reduction Between the Baseline and Treatment Periods by Drug for Children and Adults

Drug	Reference	Study group within study	Mean Effect (SE)	95% CI
Gabapentin	e-1	mITT/T/23.2-35.3/Children (3-12yrs)	0.105 (0.041)	0.025, 0.185
Gabapentin	e-2	PP/T/1200/Adult	0.115 (0.057)	0.003, 0.227
Gabapentin	e-2	PP/T/1800/Adult	0.182 (0.083)	0.019, 0.345
Gabapentin	e-3	PP/T/1200/Adult	0.215 (0.042)	0.133, 0.297
Gabapentin	e-3	PP/T/1800/Adult	0.175 (0.054)	0.068, 0.282
Gabapentin	e-4	PP/T/600-1200/Adult	0.167 (0.076)	0.018, 0.316
Gabapentin	e-4	PP/T/1200/Adult	0.141 (0.048)	0.046, 0.236
Gabapentin	e-5	PP/T/1800/Adult	0.260 (0.068)	0.126, 0.394
Gabapentin	e-5	PP/T/600/Adult	0.184 (0.066)	0.055, 0.313
Lamotrigine	e-6	ITT/M/1-15mg/kg/Children (2-16yrs)	0.312 (0.060)	0.194, 0.430
Lamotrigine	e-6	ITT/T/1-15mg/kg/Children (2-16yrs)	0.294 (0.055	0.187, 0.401
Lamotrigine	e-7	ITT/M/500/Adult	0.313 (0.063)	0.190, 0.436
Lamotrigine	e-7	ITT/T/500/Adult	0.219 (0.061)	0.100, 0.338
Lamotrigine	e-8	ITT/T/100-400/Adult	0.250 (0.070)	0.113, 0.387
Lamotrigine	e-9	PP/M/300/Adult	0.070 (0.067)	-0.062, 0.202
Lamotrigine	e-9	PP/M/500/Adult	0.160 (0.074)	0.014, 0.306
Lamotrigine	e-9	PP/T/300/Adult	0.120 (0.060)	0.002, 0.238
Lamotrigine	e-9	PP/T/500/Adult	0.280 (0.071)	0.141, 0.419
Lamotrigine	e-10	PP/T/200-400/Adult	0.352 (0.080)	0.196, 0.509
Lamotrigine	e-11	PP/T/75-400/Adult	0.361 (0.140)	0.086, 0.636

Mean and 95%CI



Pellock et al, 2012



Placebo-subtracted median percent seizure reduction between baseline and treatment periods (ranging from 7.0% to 58.6% in adults and from 10.5% to 31.2% in children) was significant for 40/46 and 6/6 of the treatment groups studied. The ≥50% responder rate (ranging from 2.0% to 43.0% in adults and from (3.0% to 26.0% in children) was significant for 37/43 and 5/8 treatment groups.

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Summary

- Based on anatomical and physiological data, from a focal seizure standpoint, physiological function of the brain of a 4 year old is similar to that of an adolescent.
- By age 4 years the EEG is quite similar to that of an adolescent and adult.
- The clinical semiology and EEG features of focal seizures in a 4 year old does not differ substantially from adolescents and adults.
- The response to AEDs in focal seizures do not differ in children older than 4 years of age than adults.