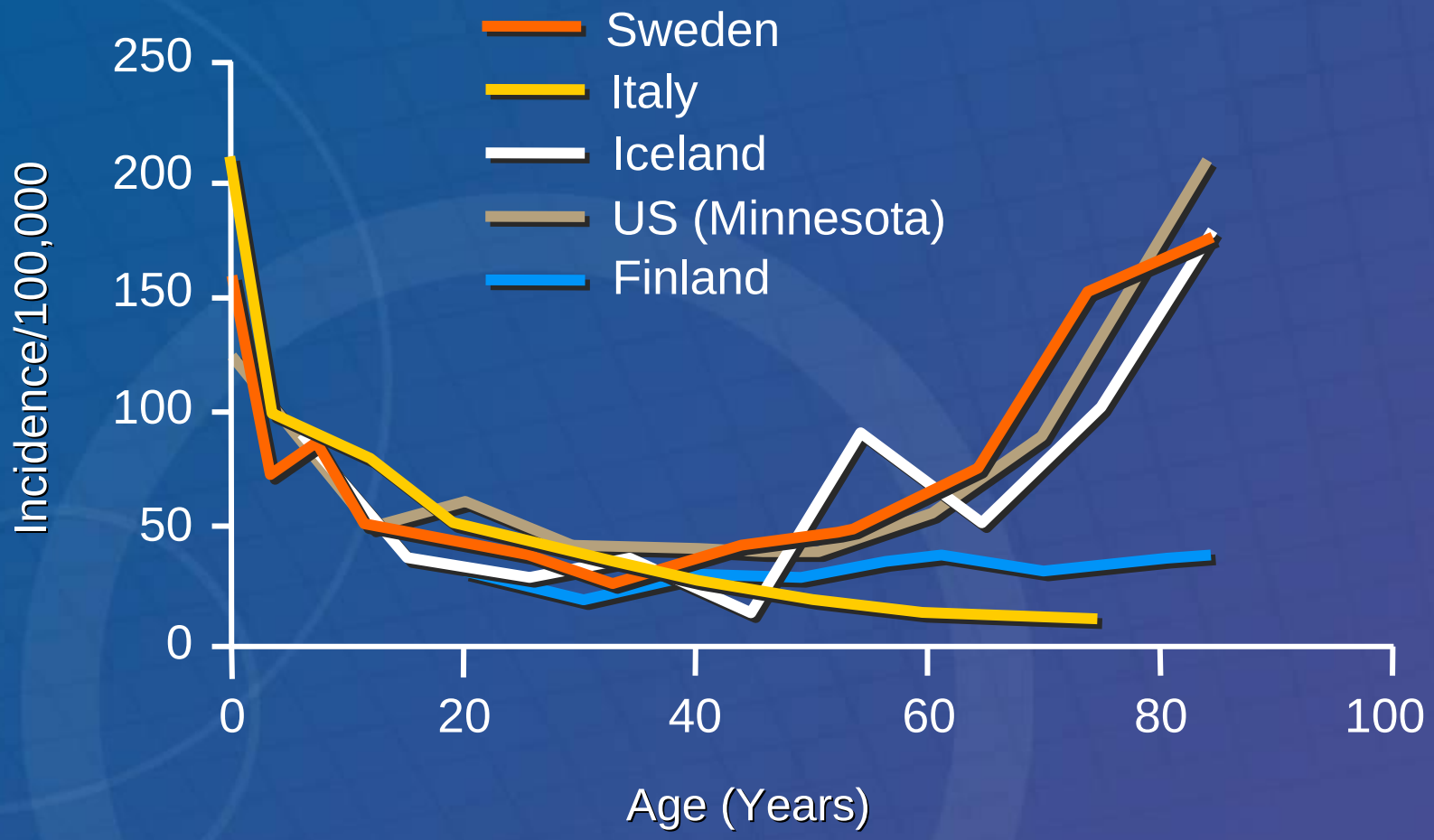
Therapeutics of the Developing Nervous System: Epilepsy as a Model

Gregory L. Holmes, MD
Department of Neurology
Dartmouth Medical School
Hanover, New Hampshire

Higher Incidence of Epilepsy in the Young and Elderly

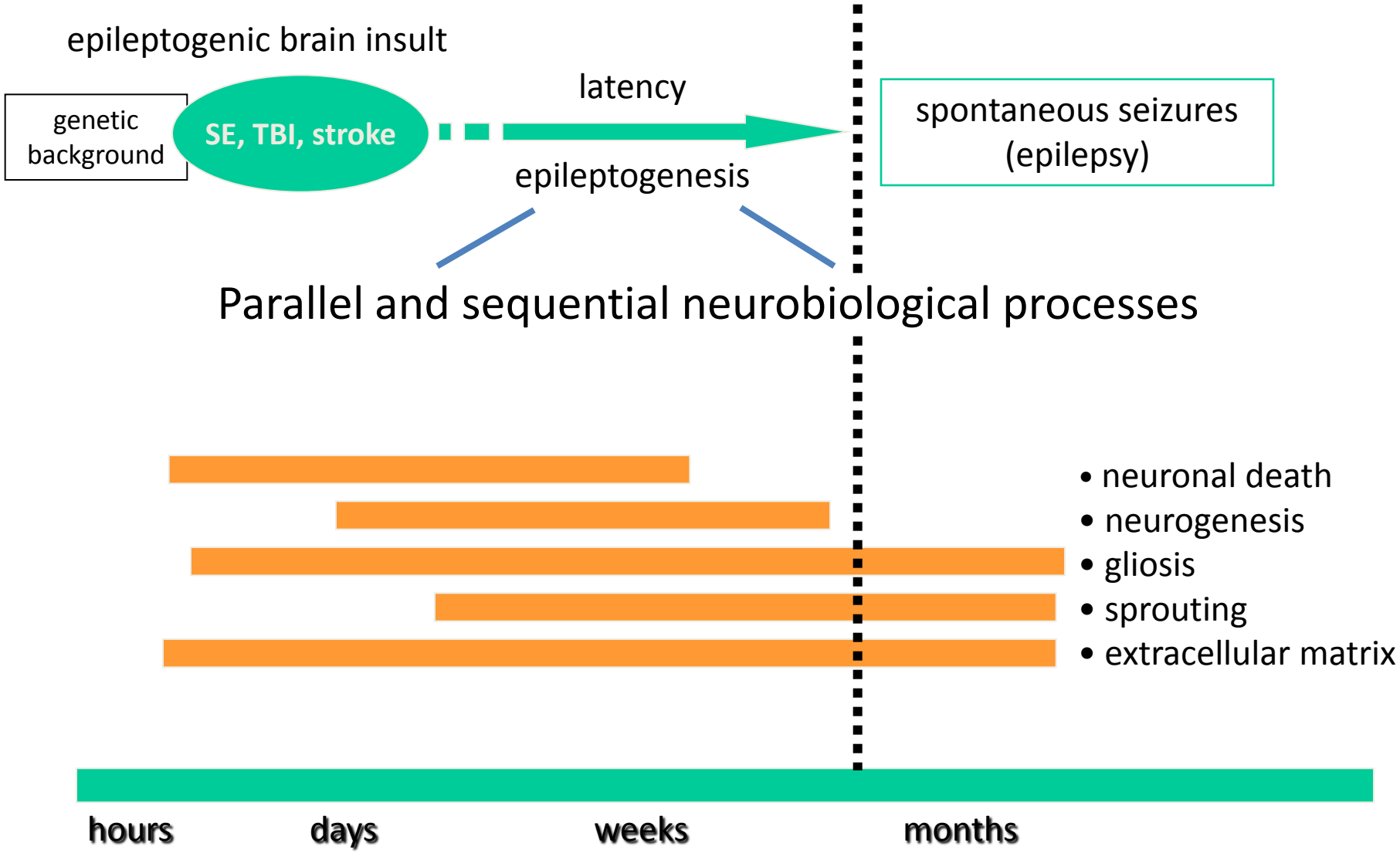


Adapted from Hauser. In: *Epilepsy: A Comprehensive Textbook*. 1997.

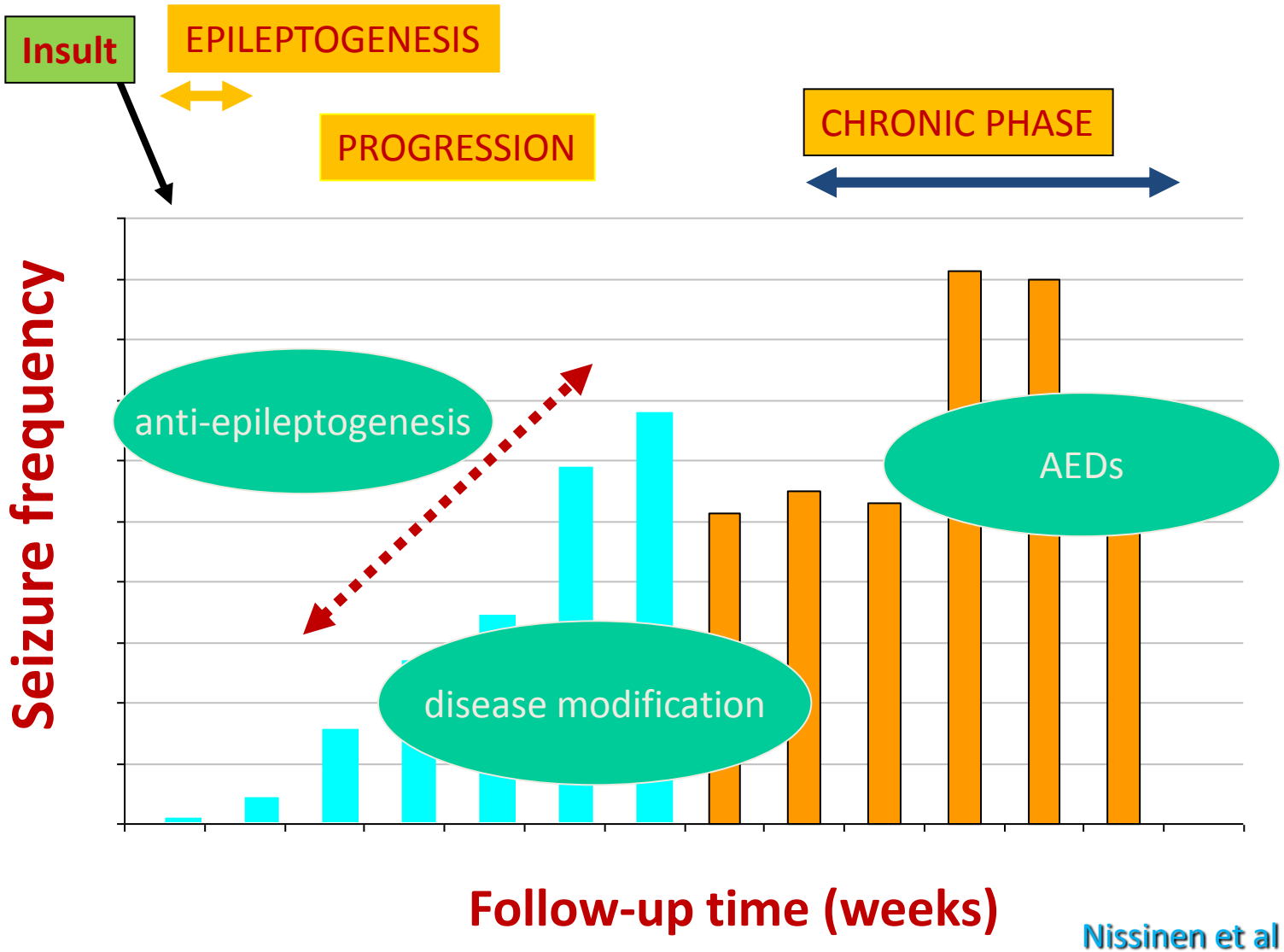
Targeting Epilepsy

- Prevention of epileptogenesis
- Treating seizures
  - Status epilepticus
  - Spontaneous recurrent seizures
- Treating consequences of seizures

Acquired Epileptogenesis



Progression of Epileptic Process in Rat



Nissinen et al (2000)

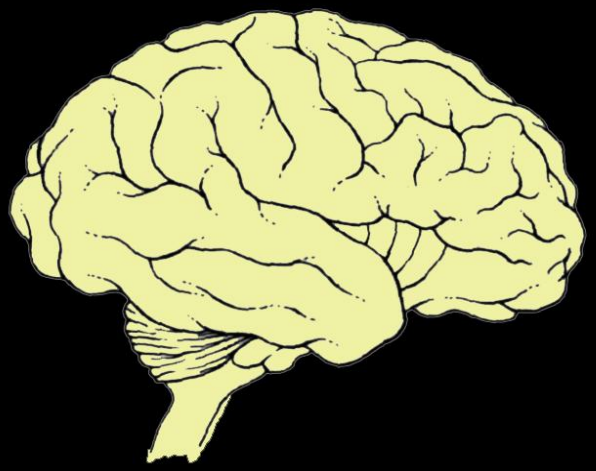
Animal Models of Seizures - Acquired

- Electrical
  - Maximum electrical shock
  - Self-sustainin status epilepticus
  - Kindling
- Chemoconvulsant
  - Pentyleneterazol
  - Bicuculline
  - Picrotoxin
  - Kainic acid
  - Pilocarpine
  - Flurothyl
- Chemo-non-convulsive
  - γ-hydroxybutyrate
  - THIP
  - Peniciillin
- Hyperthermia
- Chemical Kindling
  - Pentylenetetrazol
  - Picrotoxin
  - Bicuculline
  - Beta carboline
- Hypoxia
- Focally injected convulsants
  - Aliumina gel
  - Tetanus toxin
  - Cephalosporins
  - Iron
  - Penicillin
- Trauma
- Stroke
- Radiation

Animal Models of Seizures - Genetic

- Spontaneous single-locus mouse mutants
  - Spike-wave
    - Tottering
    - Lethargic
    - Ducky
    - Stargazer
  - Convulsive
    - Jimpy
    - Jittery
    - Quaking
    - Staggerer
    - Torpid
  - Convulsions evoked by sensory stimuli
    - Frings
    - Lurcher
- Spontaneous seizures and developmental disruptions
  - Flathead rat
  - Tish rat
- Models of Absence
  - WAG/Rij
  - Strasbourg
- Transgenic and targeted gen knockout models
  - $AKv_{1.1a}$-K^+
  - Gabb1
  - Gabb3
  - Kcna1
  - Lcnq2
  - Scn1b
  - Scn2a

Proliferation



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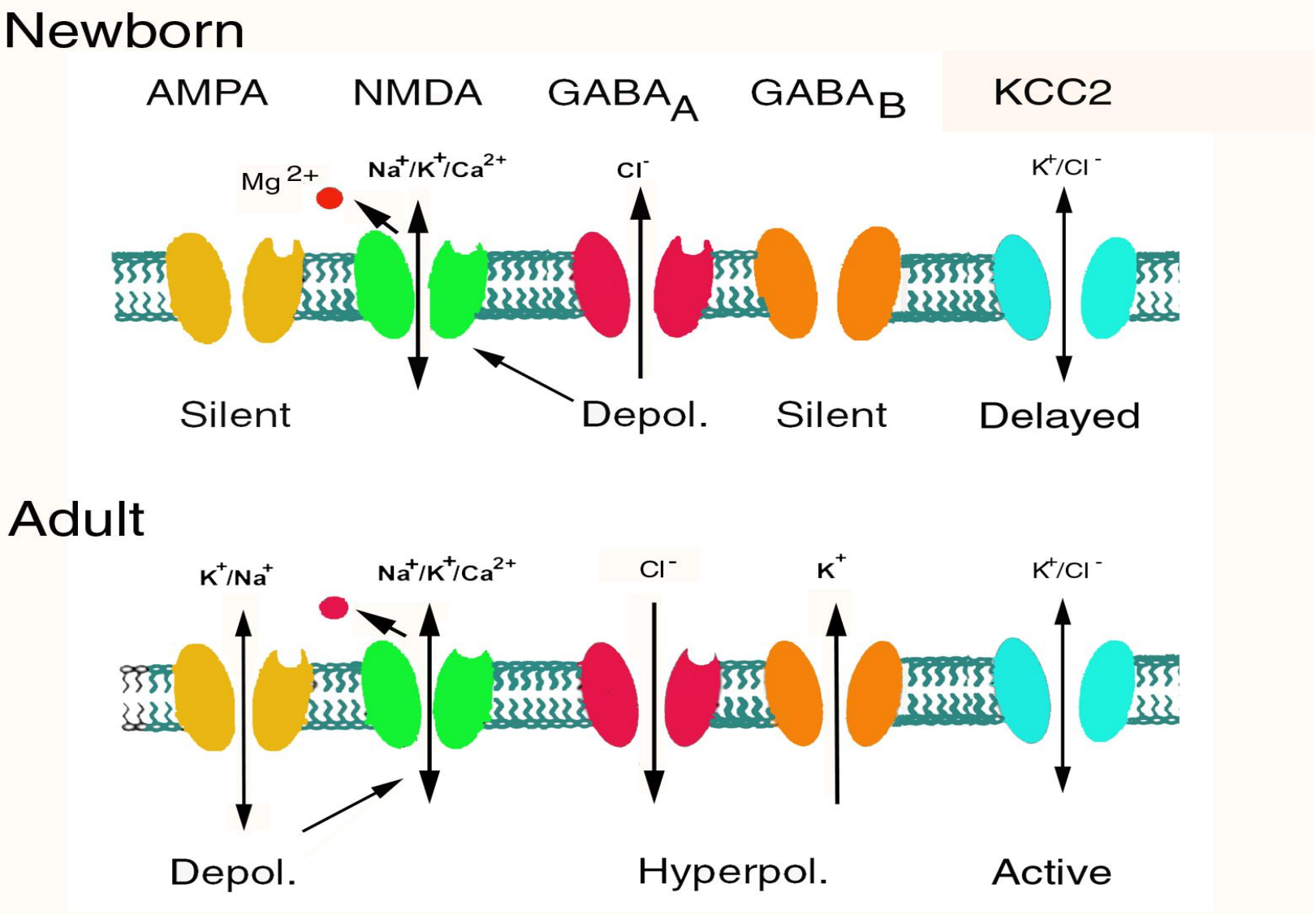
9 MONTHS **ADULT**

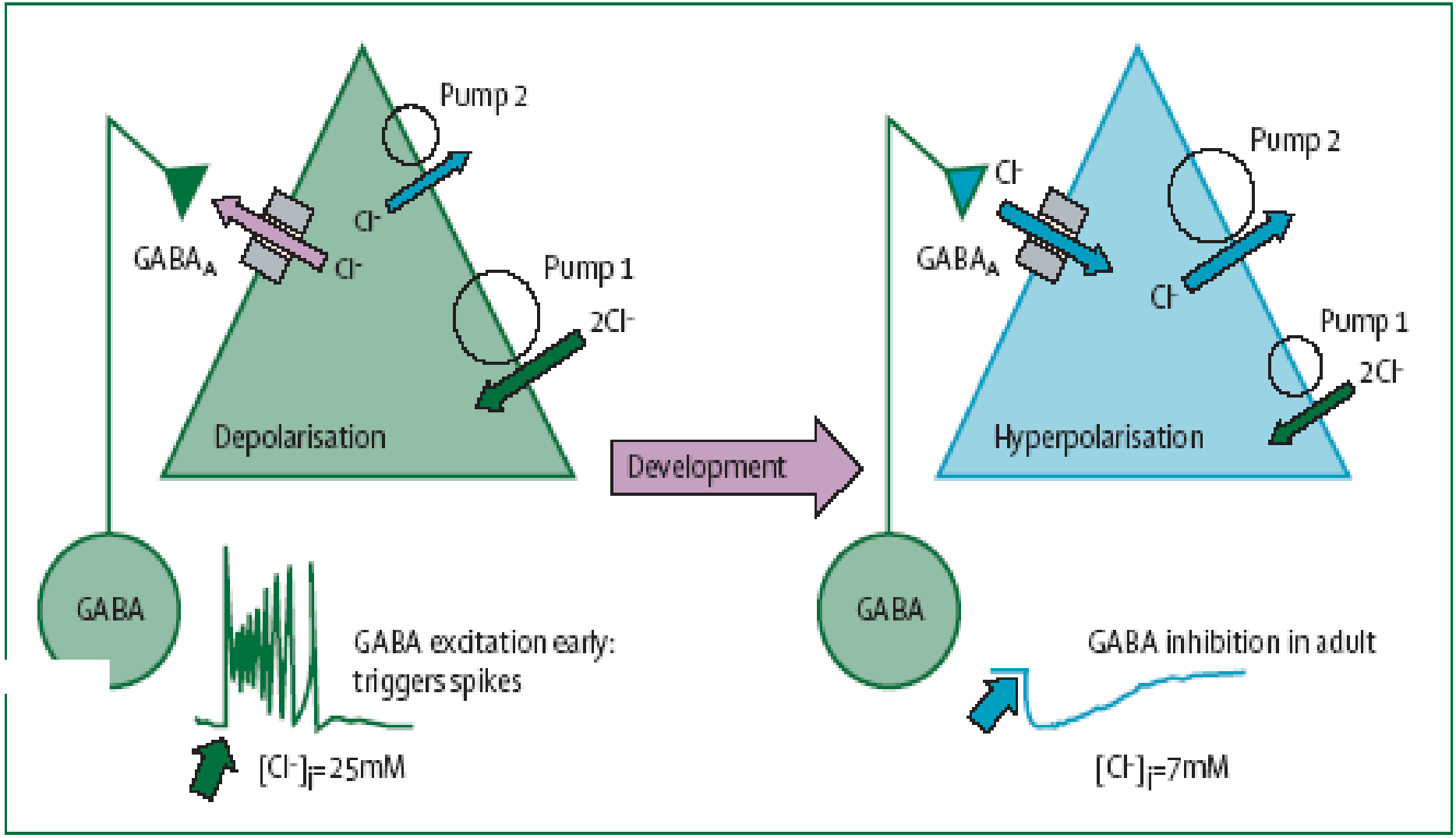
Conception

270 Days

Gestation

Developmental Aspects of Receptor Development

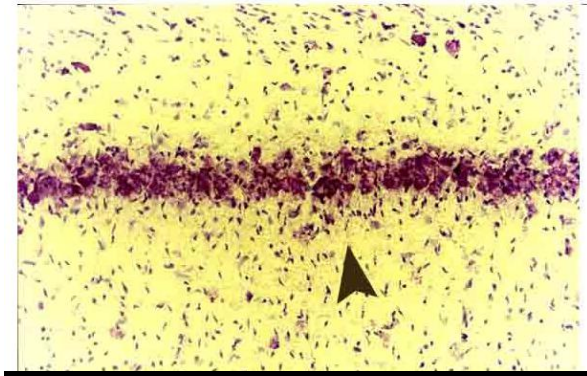


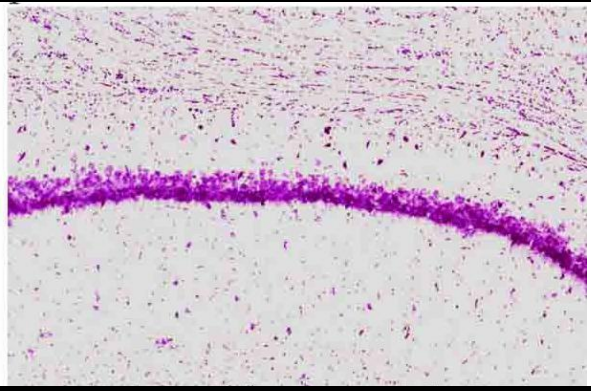

Pump 2
Cl-
GABA$_A$
Cl-
Pump 1
2Cl-
Depolarisation
Development
GABA
GABA excitation early:
triggers spikes
[Cl-]$_i$= 25mM
Cl-
Pump 2
GABA$_A$
Cl-
Pump 1
2Cl-
Hyperpolarisation
GABA
GABA inhibition in adult
[Cl-]$_i$=7mM

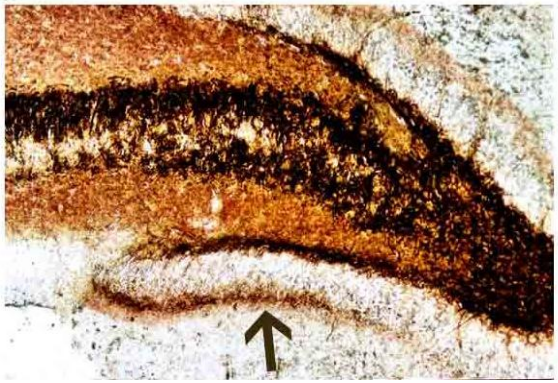
Flurothyl Model of Neonatal Seizures

Adult Sz

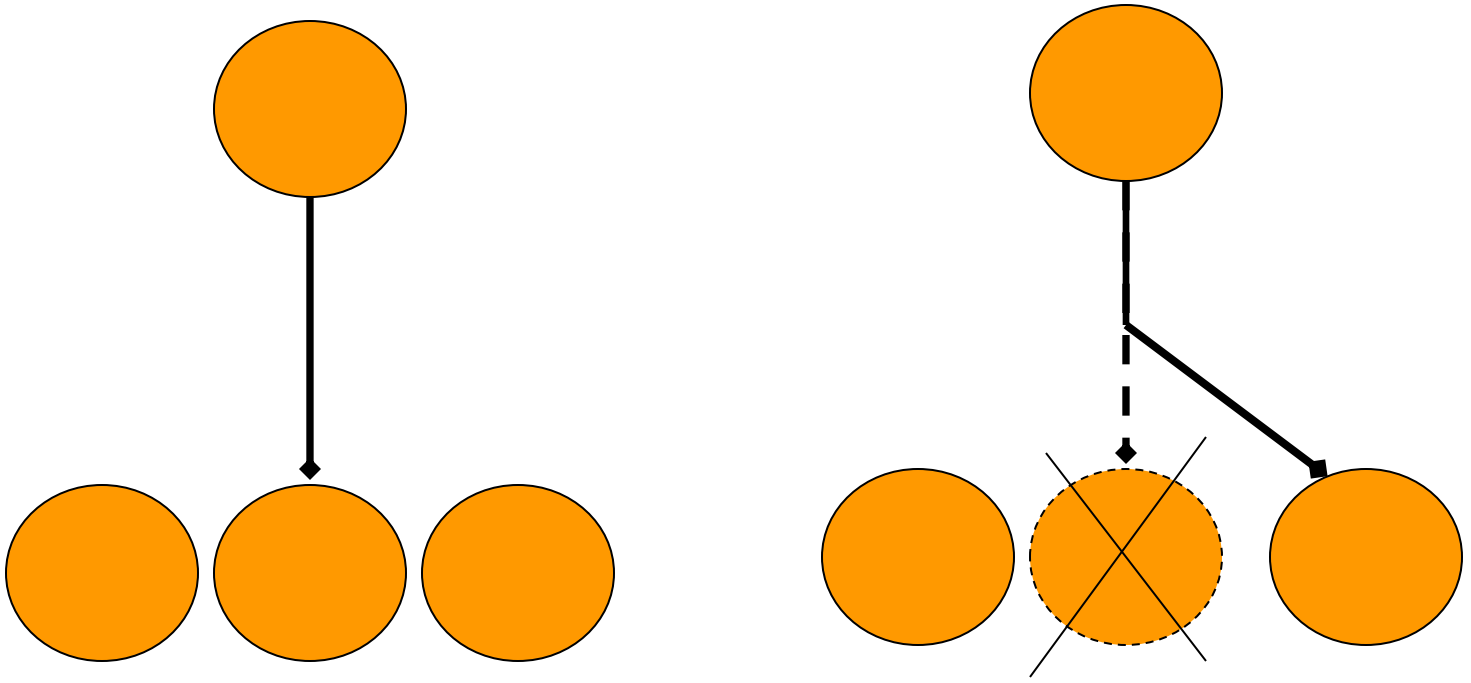
Early Life Sz



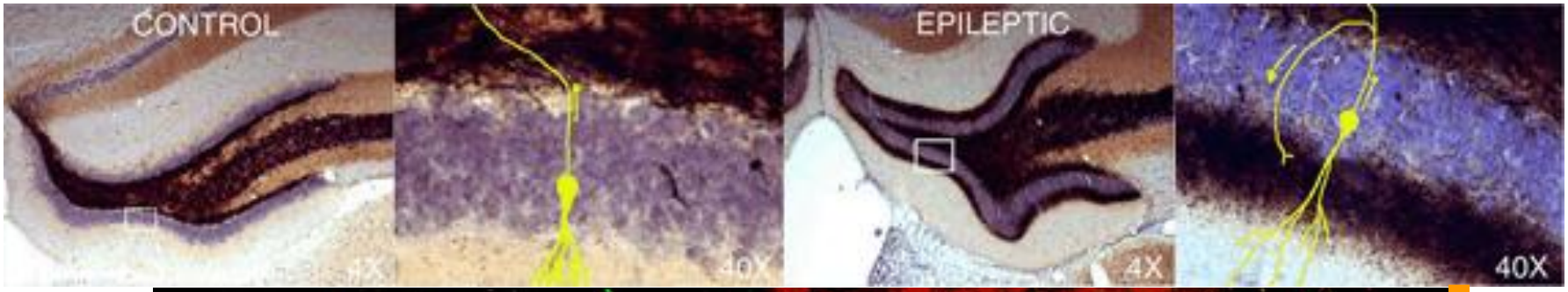


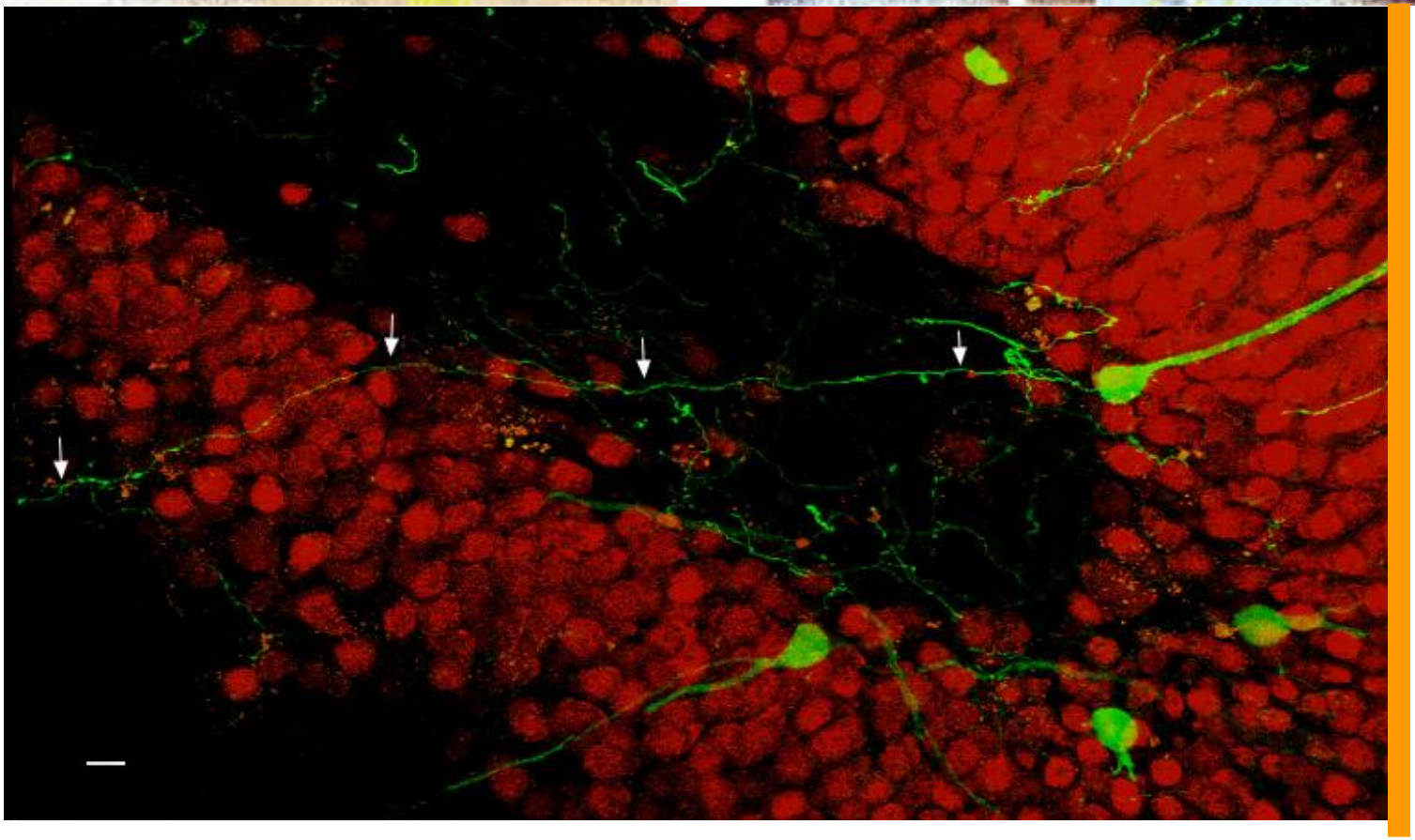


Sprouting



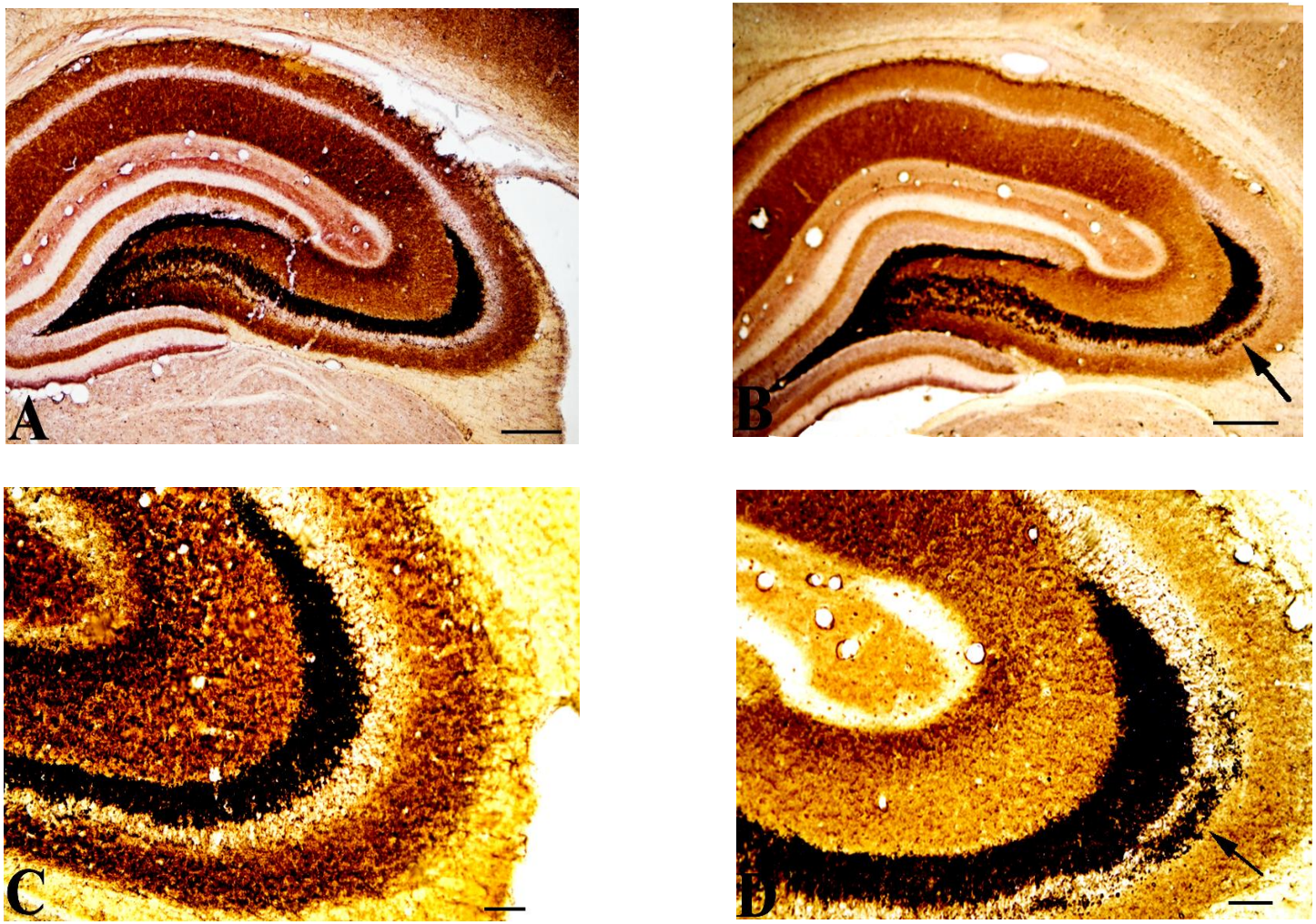
Aberrant Sprouting





Thuret Laboratory Website

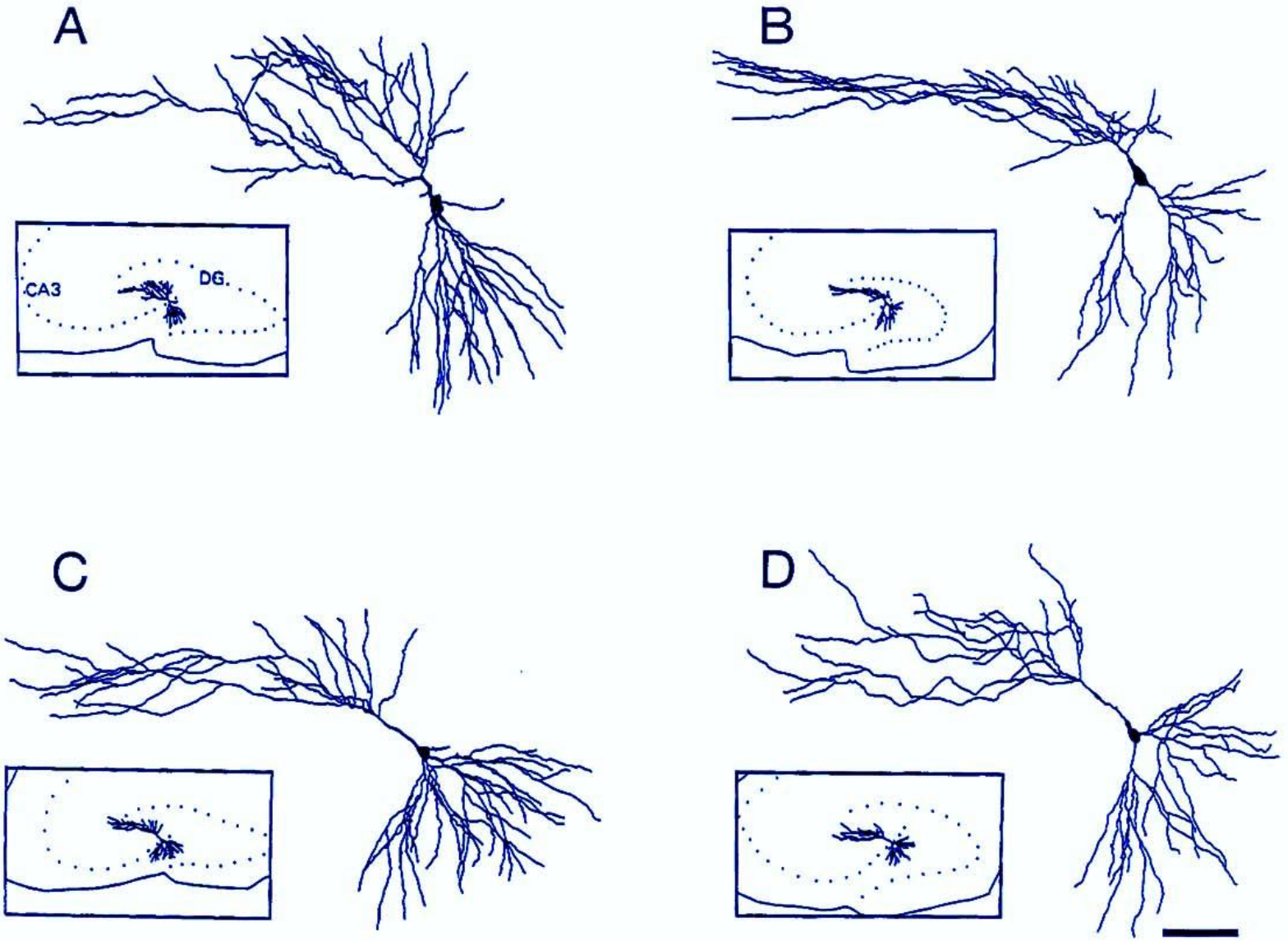
Mossy Fiber Sprouting Following Neonatal Seizures



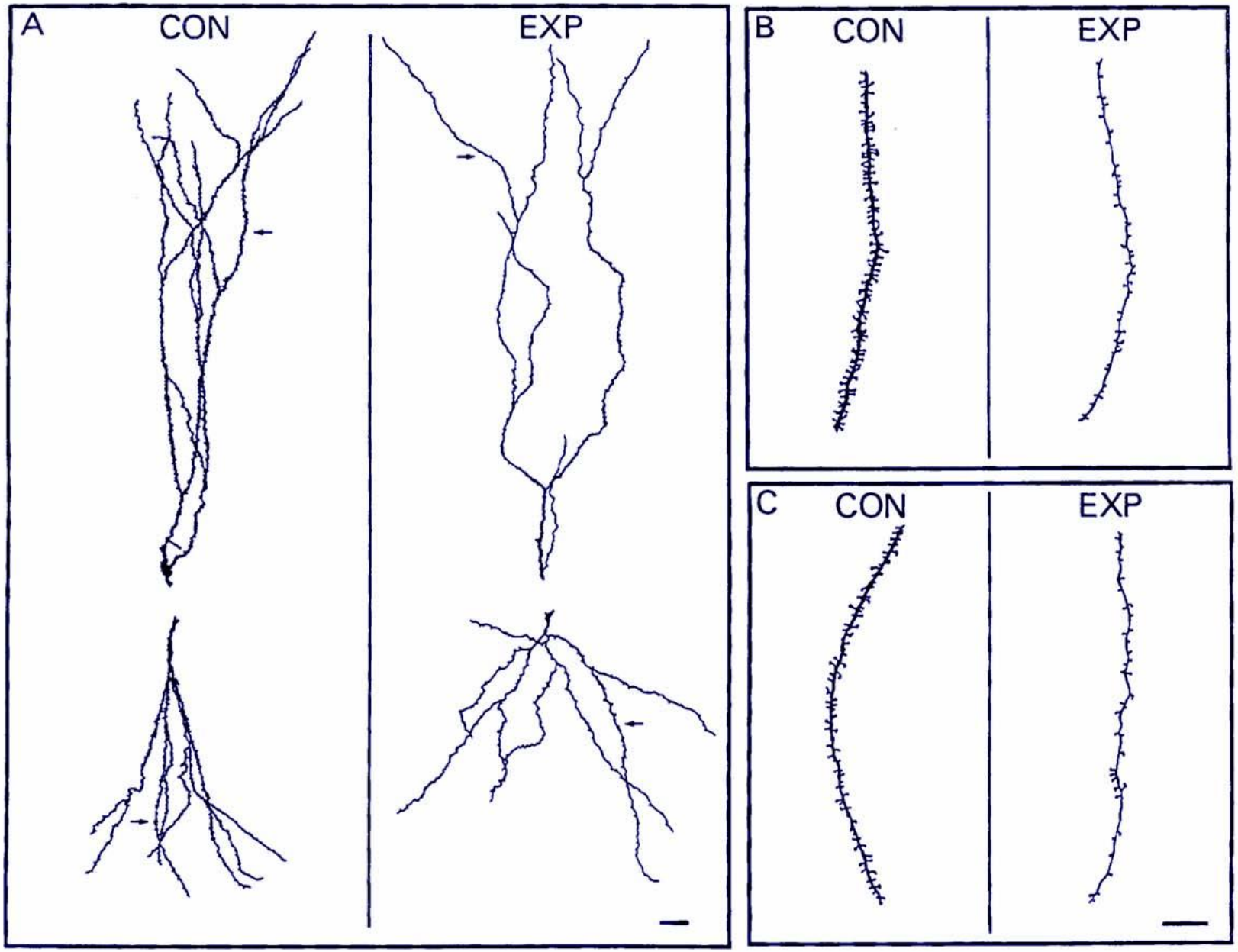
Holmes et al., 1999

Controls

Early-life seizures

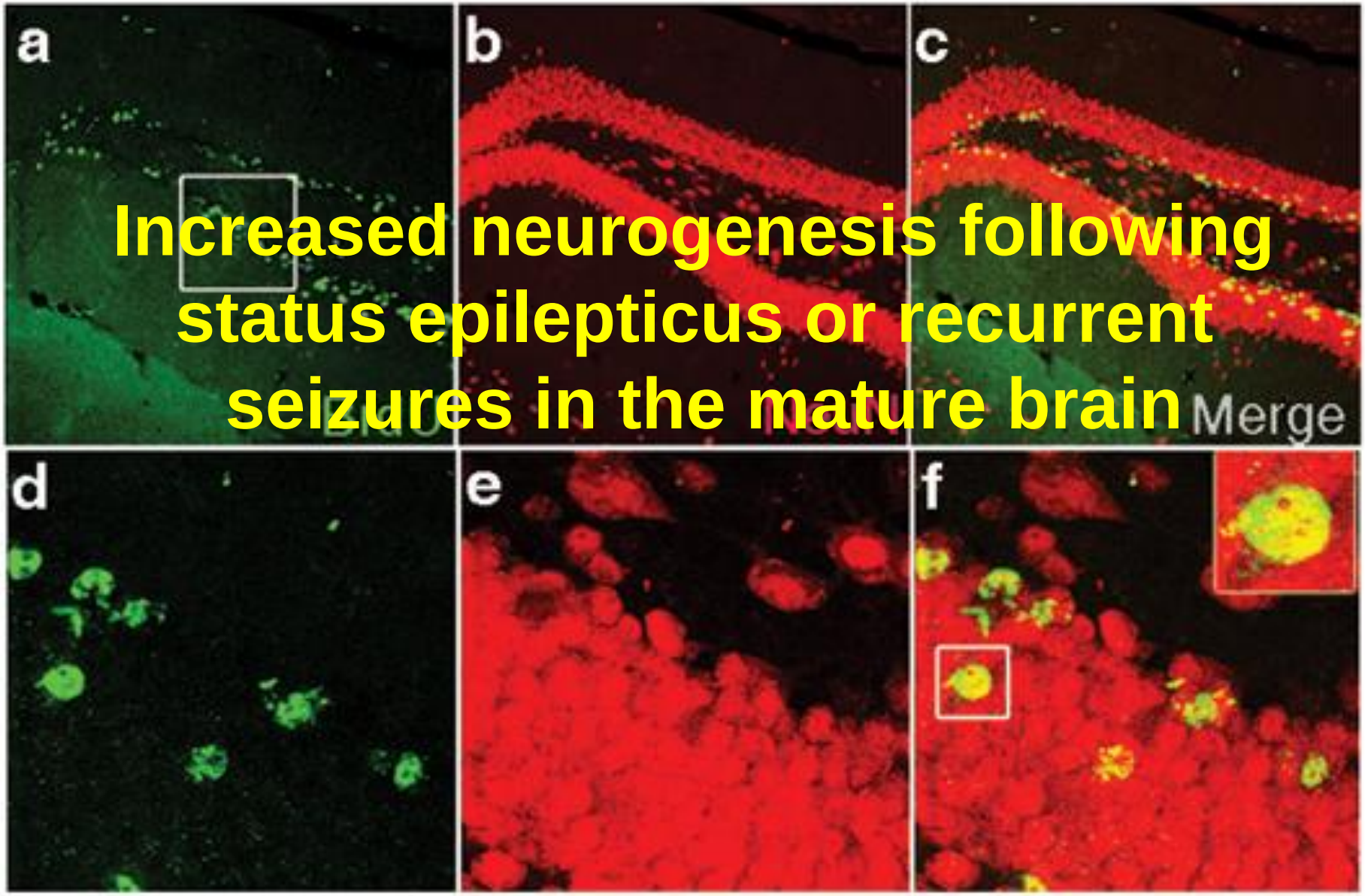


Jiang et al., 1998



Jiang et al., 1998

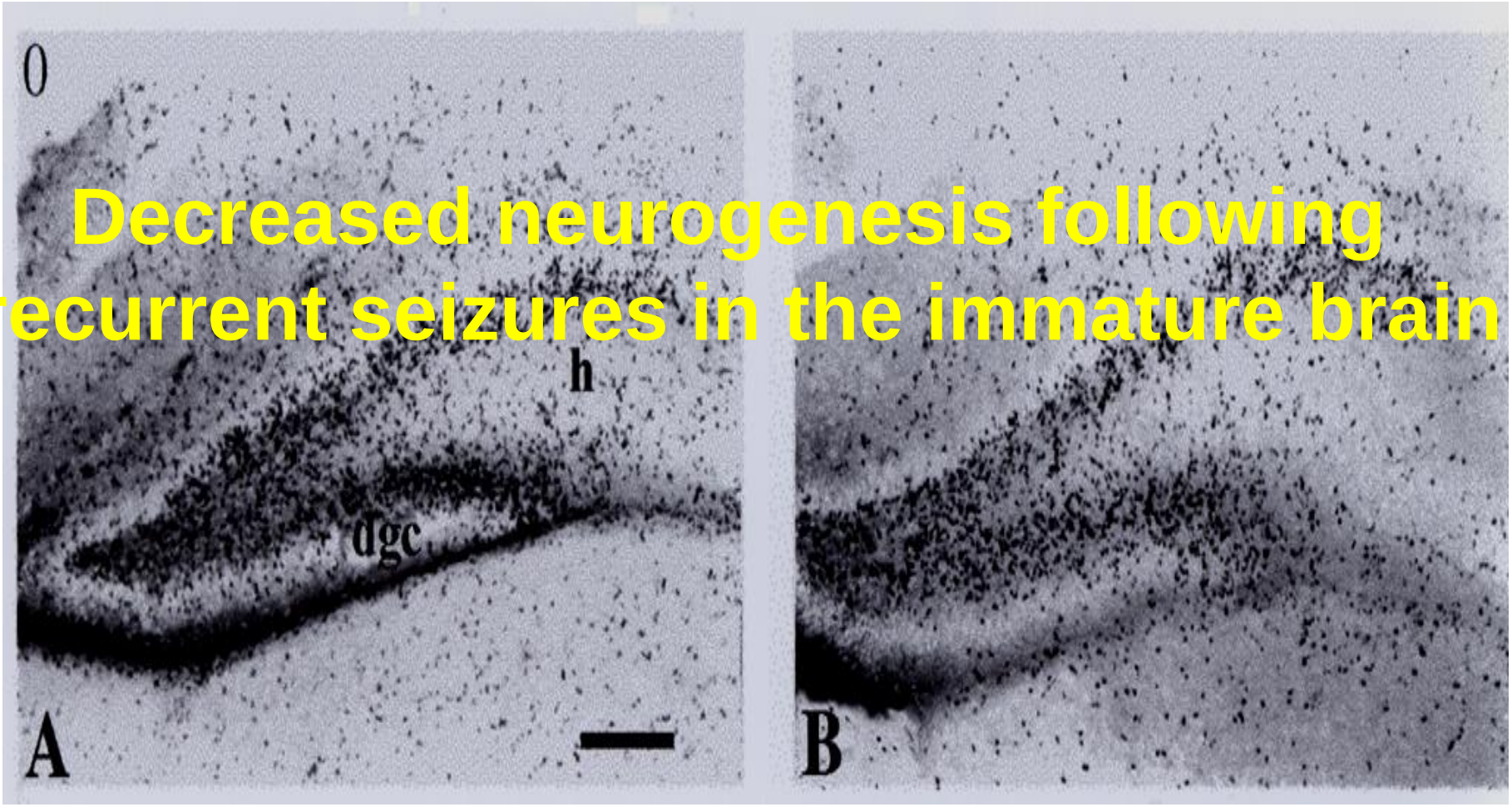
Neurogenesis



Increased neurogenesis following status epilepticus or recurrent seizures in the mature brain

Coulter Laboratory Website

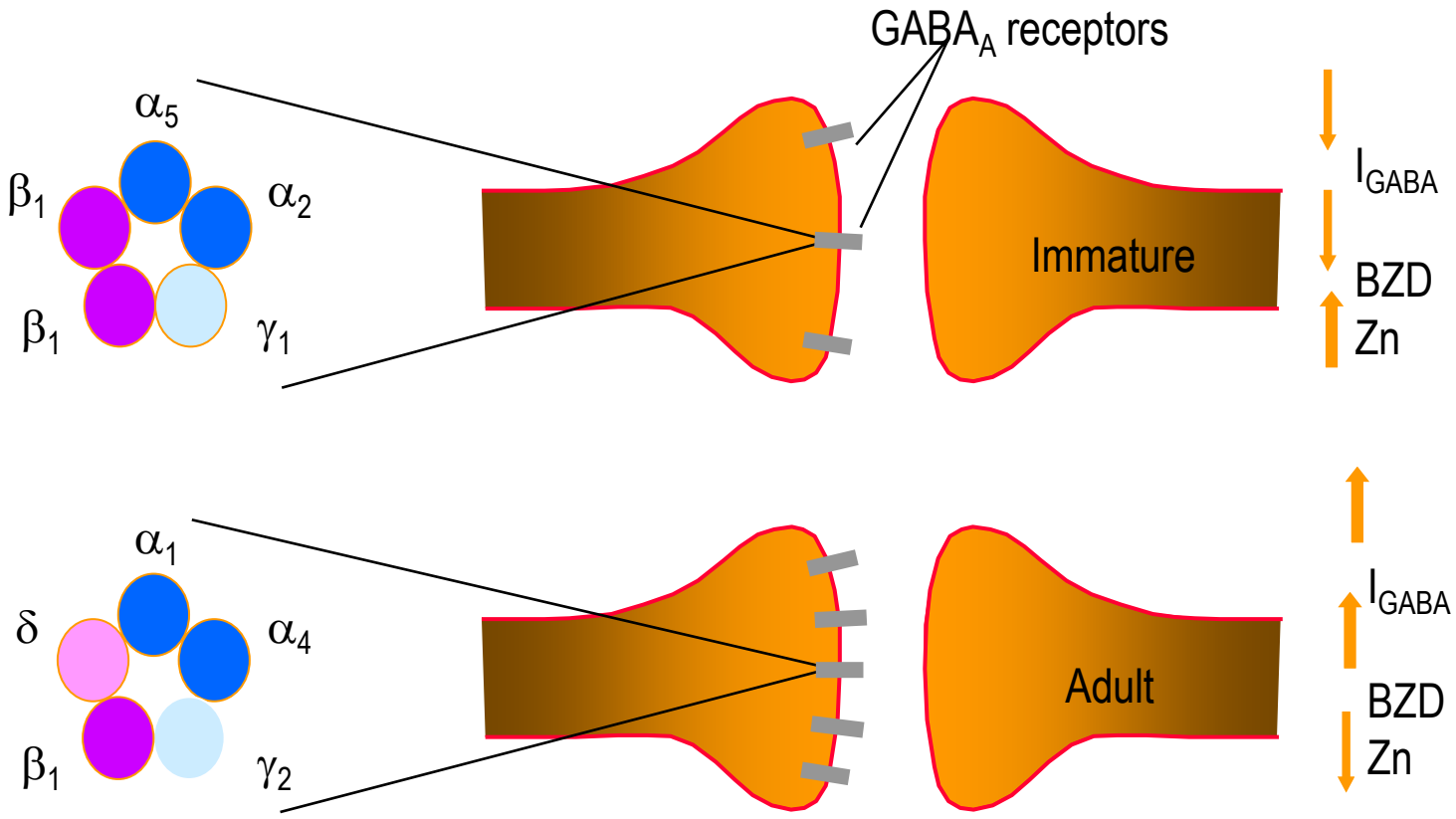
Neurogenesis Following Neonatal Seizures



Decreased neurogenesis following recurrent seizures in the immature brain

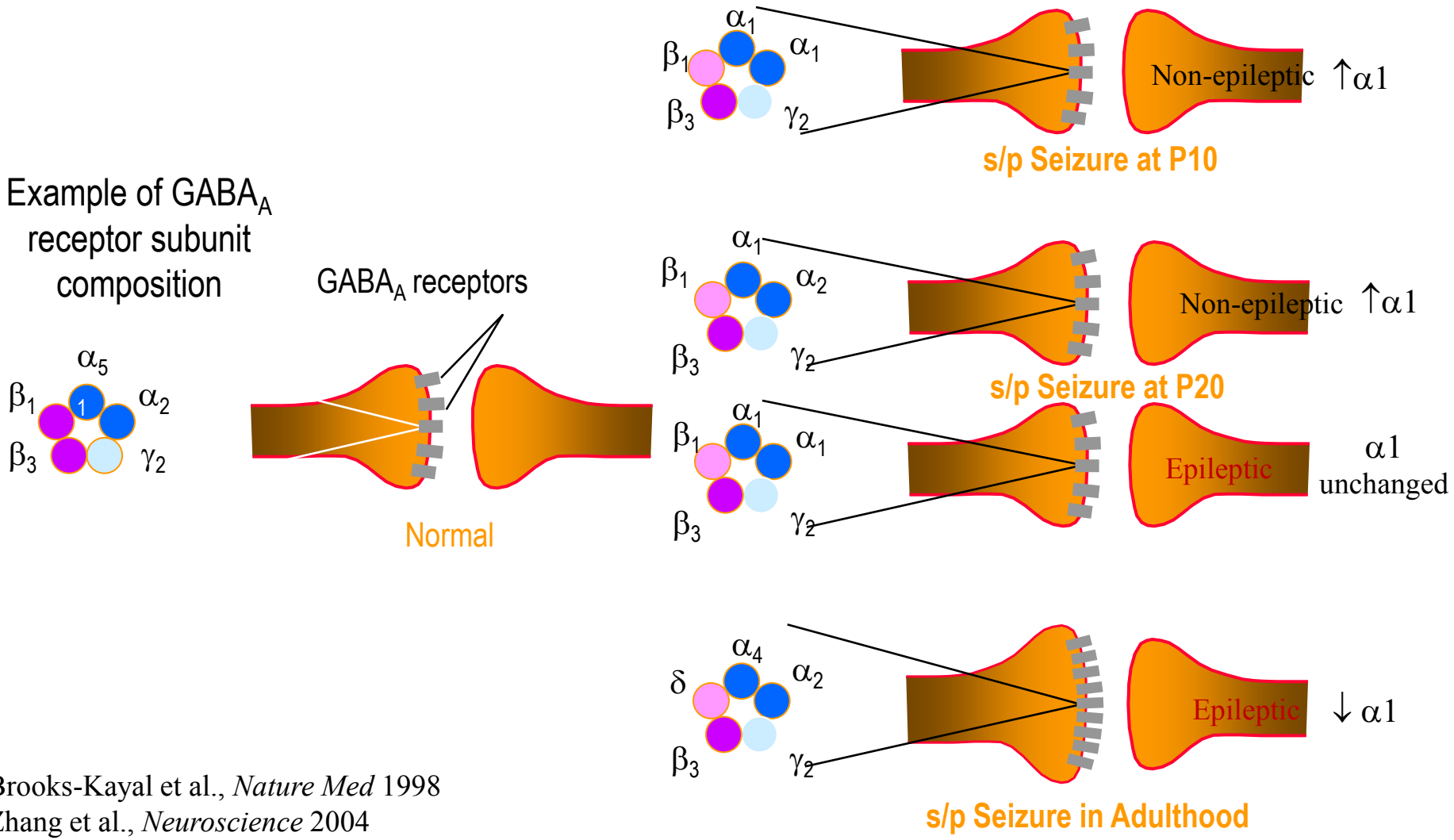
McCabe et al. 2000

Developmental Changes in $GABA_A$ Receptor Expression and Function



1. Killisch et al., 1991; Laurie et al., 1992; Wisden et al., 1992; Fritschy et. al., 1994. 2. Brooks-Kayal et al., 200
3. Gibbs et al., 1996; Hollrigel & Soltesz, 1997; Dunning et al., 1999; Kapur & Macdonald, 1999

Seizures at Different Ages Cause Distinct Patterns of Inhibitory Changes

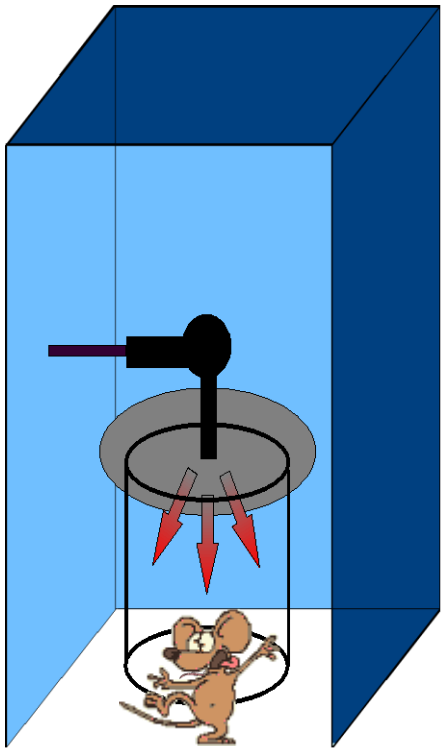


Brooks-Kayal et al., *Nature Med* 1998
Zhang et al., *Neuroscience* 2004

Epileptic Encephalopthies

- Concept is that the **seizures, EEG abnormalities**, or both, contribute to the **encephalopathy** in **children**.
- Conditions
  - Landau-Kleffner
  - Continuous spike-wave of sleep (ESES)
  - Infantile spasms
  - Lennox-Gastaut syndrome

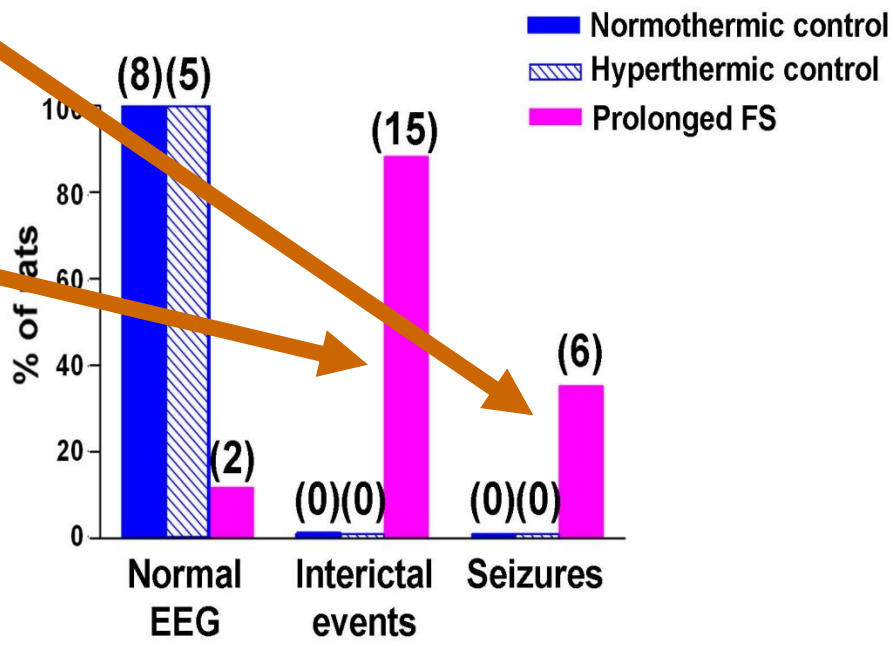
Immature Rat Model of Prolonged Febrile Seizure



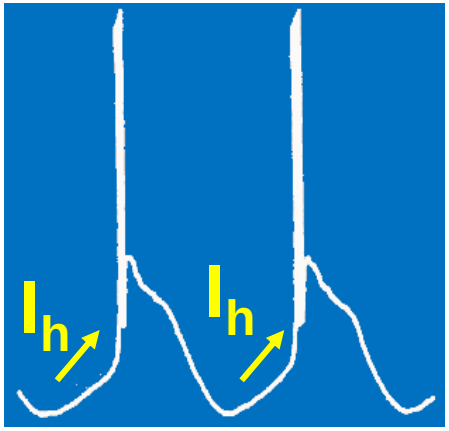
- Age appropriate
- Physiological temps
- >98% seizure induction
- EEG validated
- Controlled seizure duration
- Fever mediators involved
- No mortality

Prolonged Febrile Seizures May Be Epileptogenic

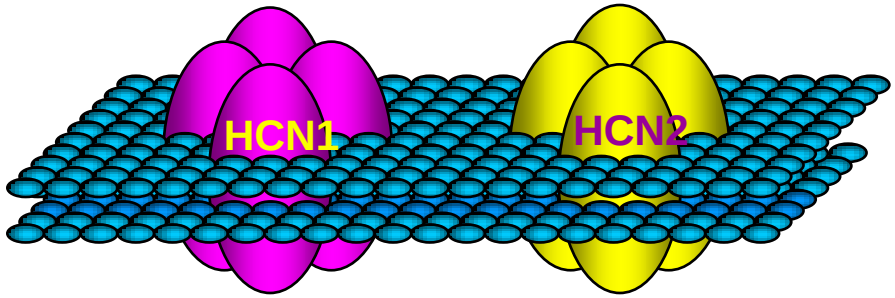
- Epilepsy in 35%
- EEG abnormalities in many
- High sensitivity to convulsants
- Hyper-excitable hippocampus



Molecular Basis for Febrile Seizure-Induced Changes



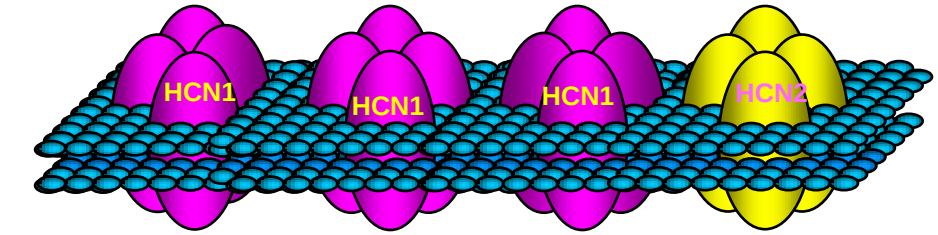
Hyperpolarization activated cyclic-nucleotide gated



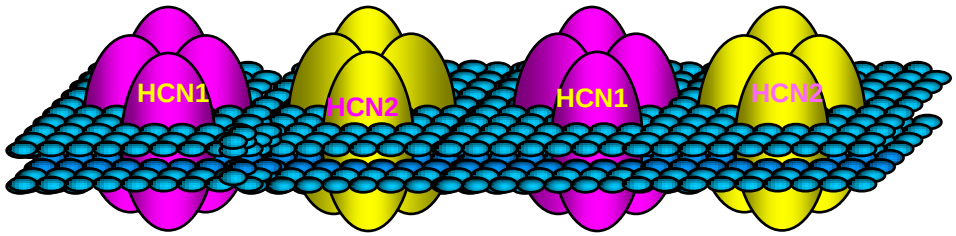
Channel consists of 4 (homomeric) subunits

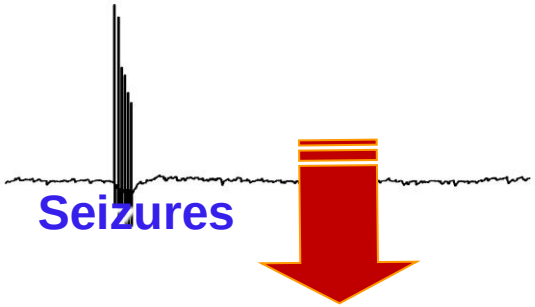
	HCN1	HCN2
Major Location	Hippocampus Brainstem	Thalamus Hippocampus
Location	Fast kinetics Modest cAMP gating	Slow kinetics

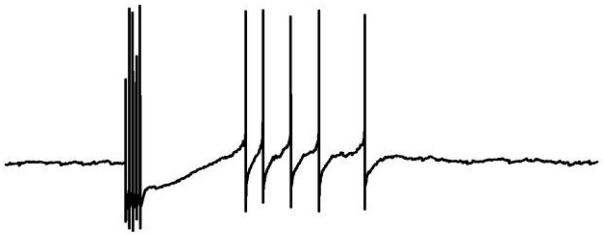
Seizures Reduce HCN1 Resulting in Increased Excitability



Seizures

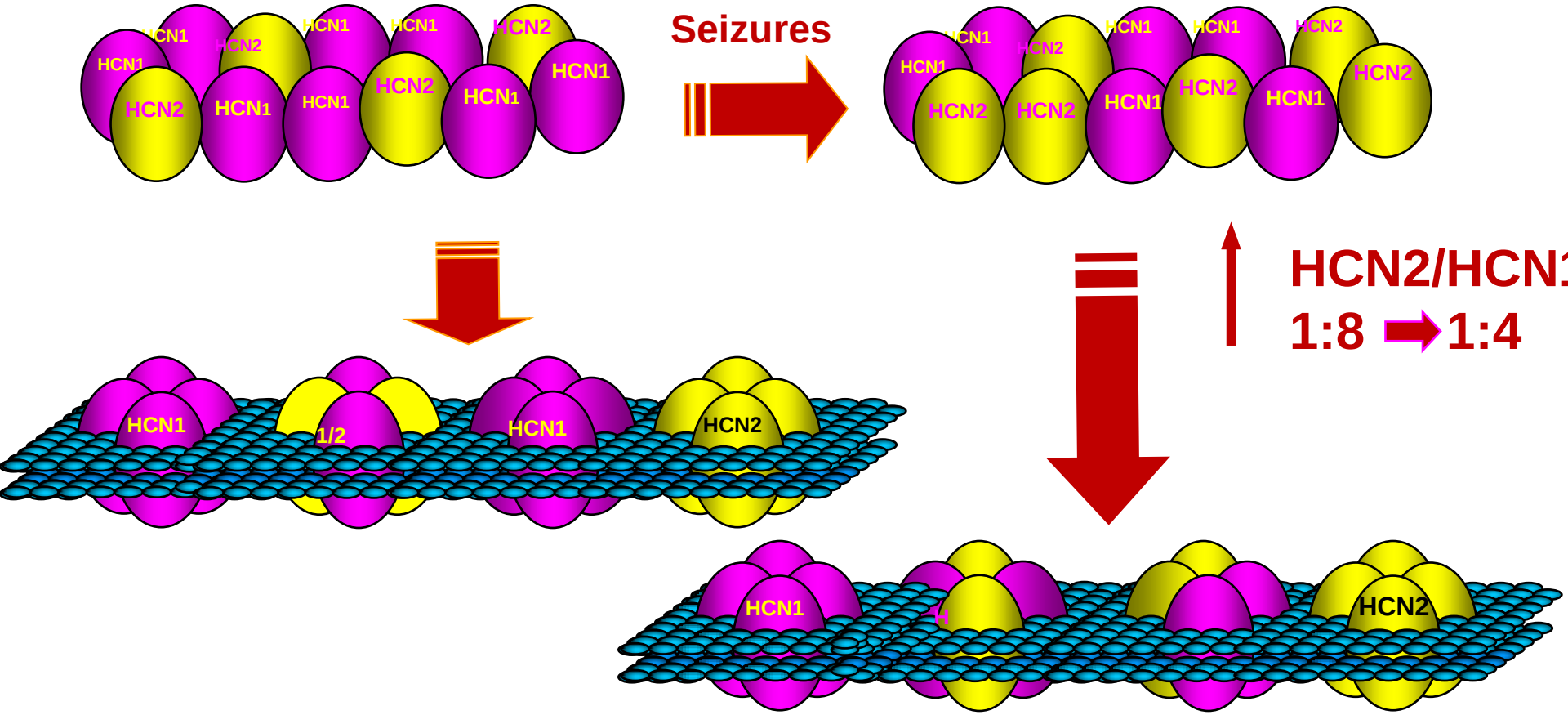


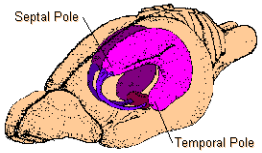




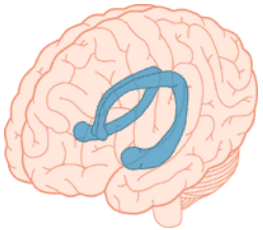
Chen et al., 2001;Brewster et al., 2002; Santoro & Baram 2003

Seizure-Evoked Rearrangements of HCN Channels



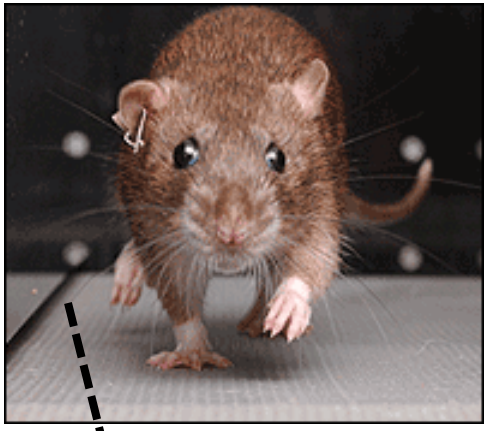


Theta Rhythm

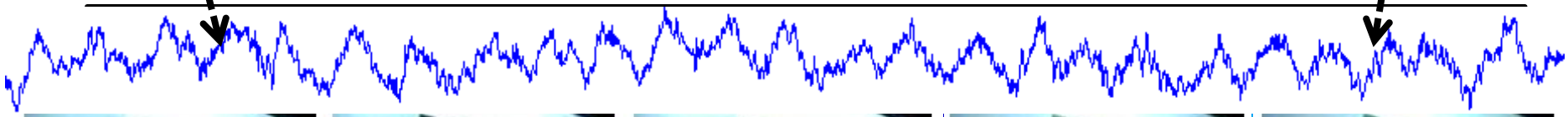


Rats: 4-12Hz

Humans: 4-8Hz



1 second

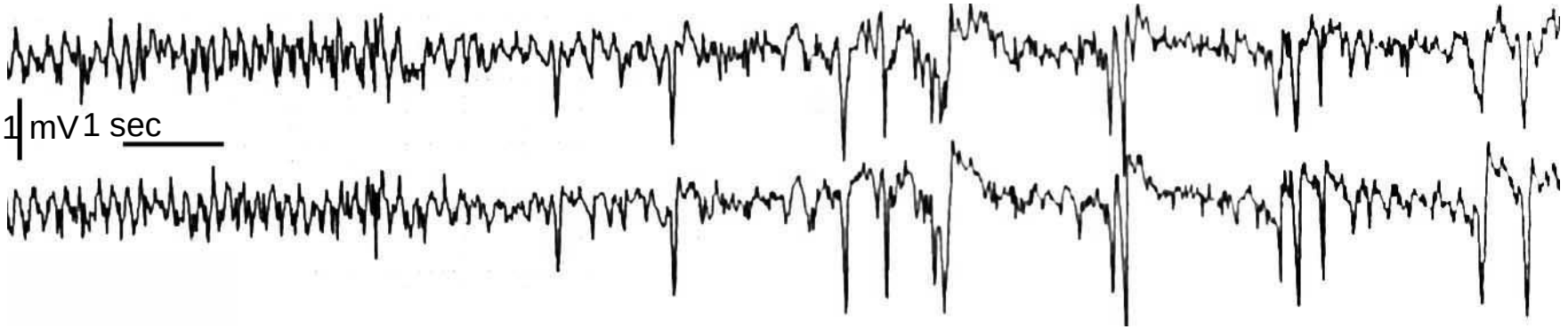


Time-locked to lever pressing behavior (Sample & Match presses)

Hippocampal Theta Oscillations

Walk

Immobile



Theta

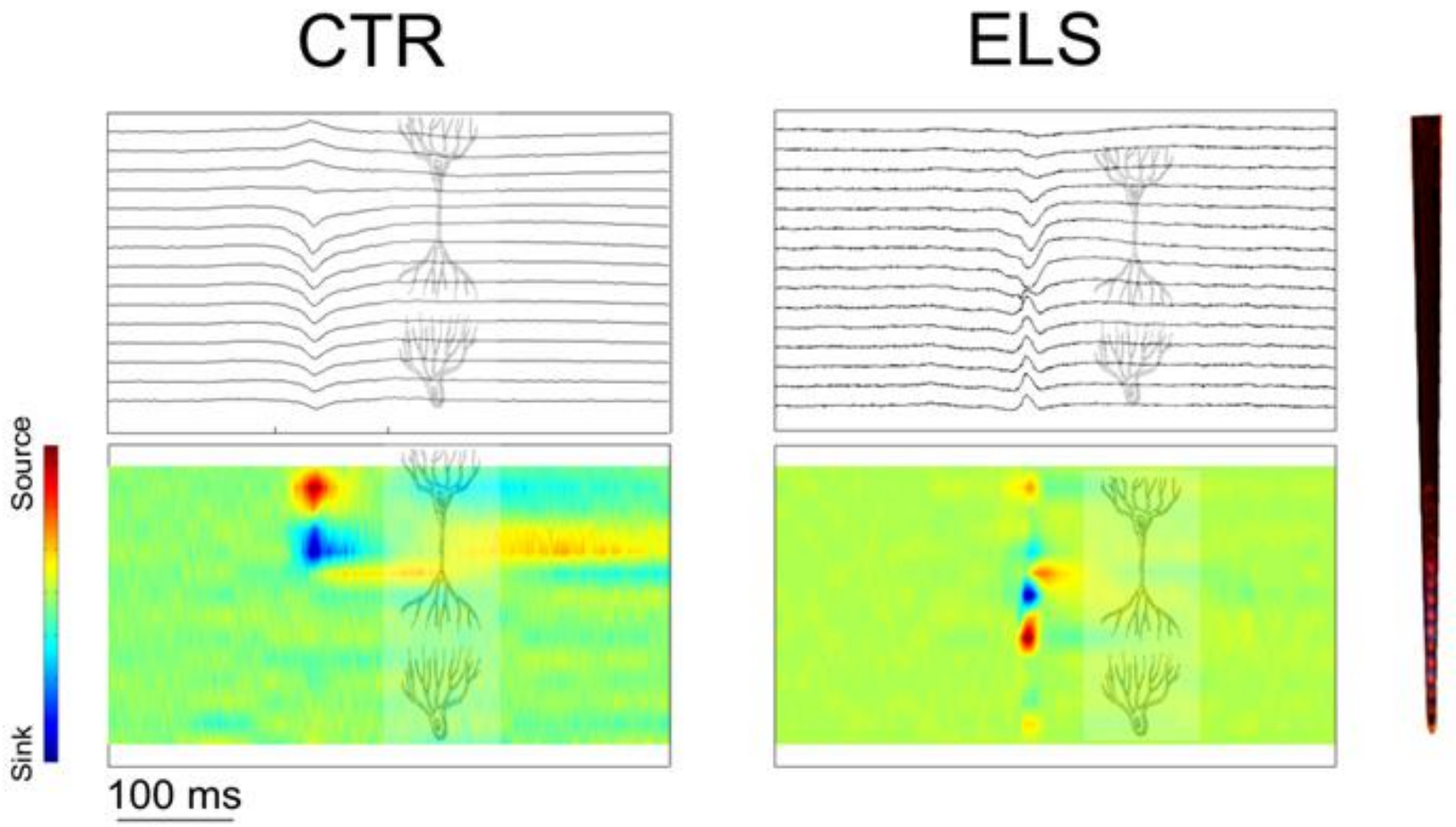
LIA

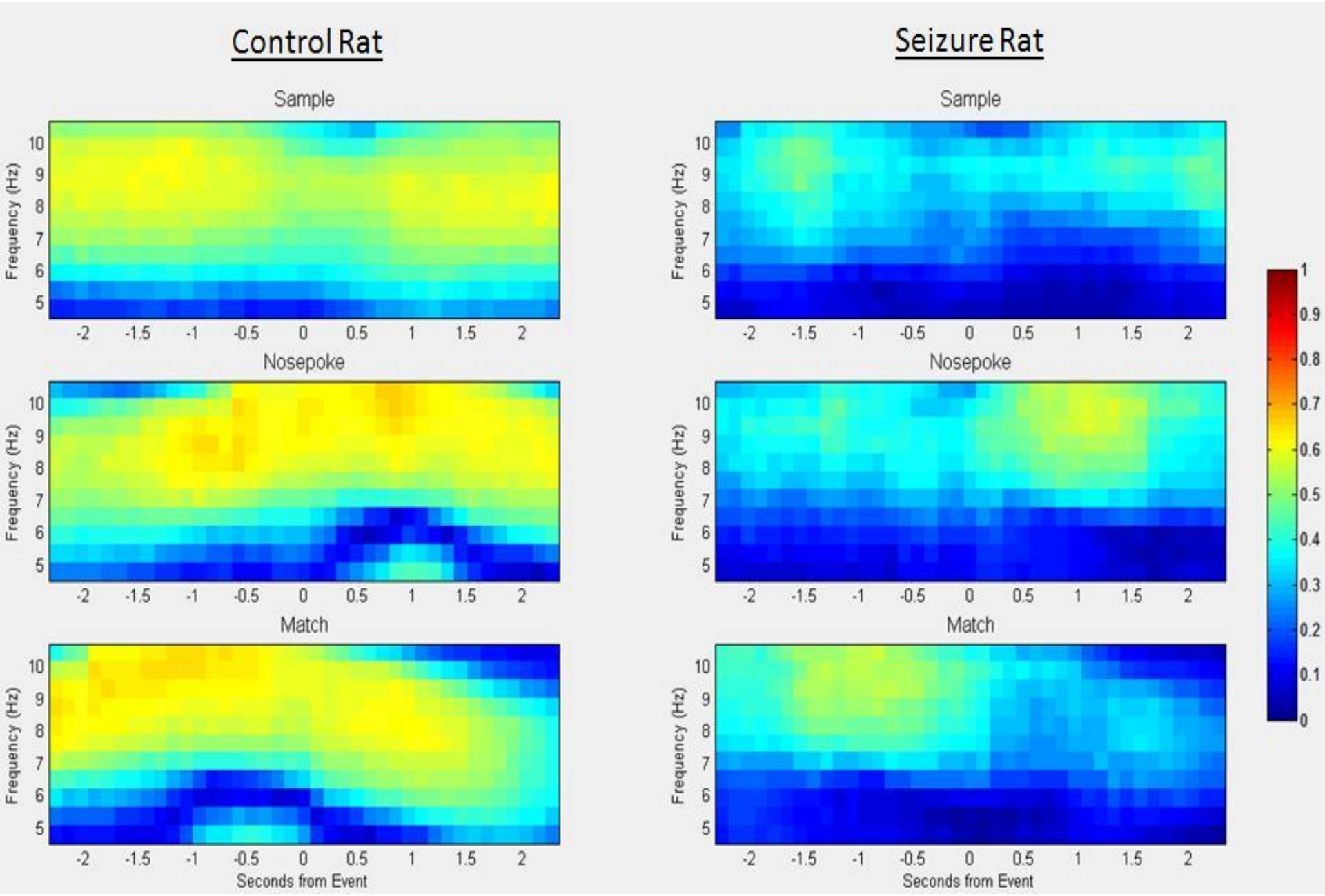
exploration

consummatory behaviors, immobility, grooming

Buzsaki, Neurosci. 1989

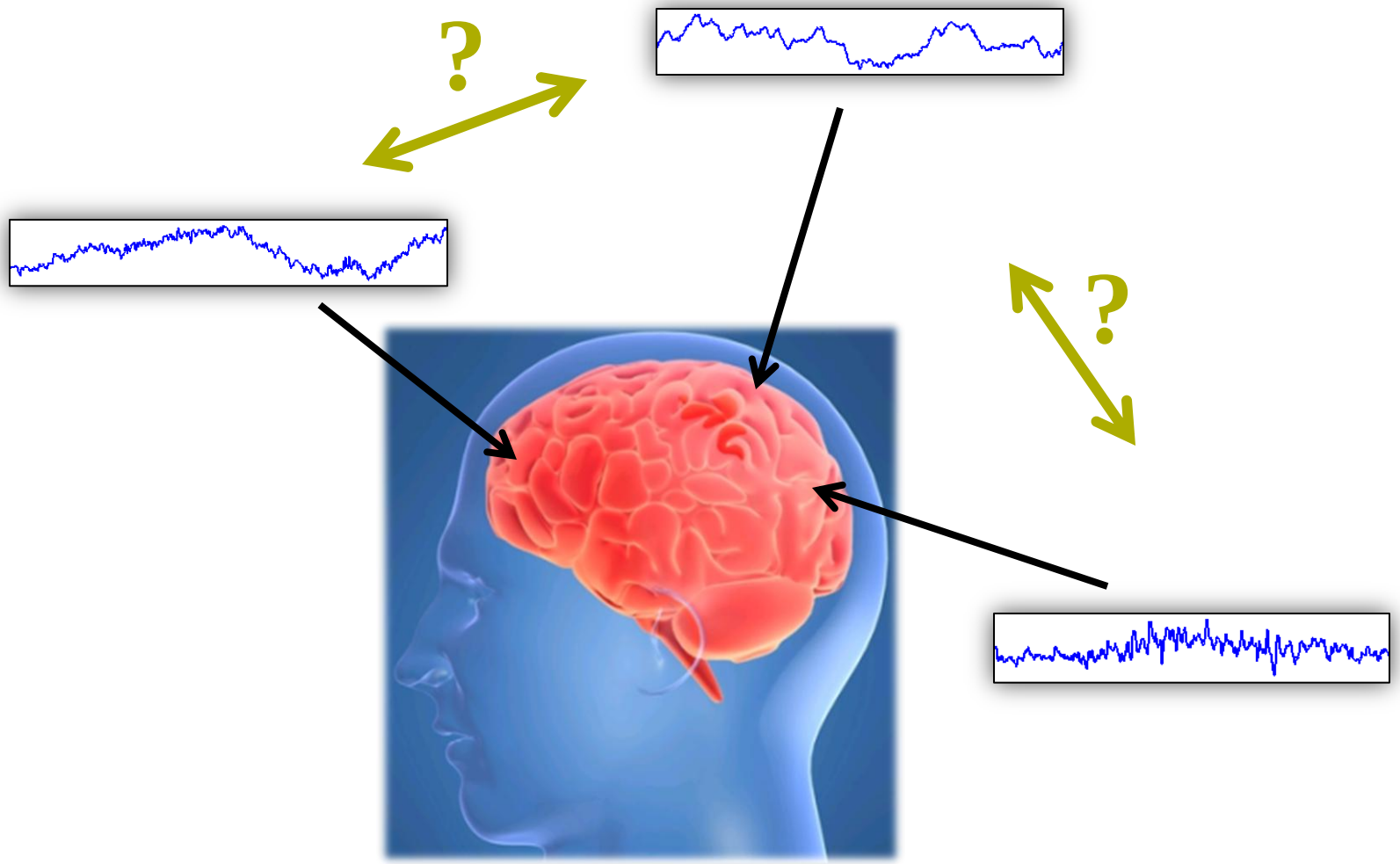
Changes in Source and Sink with Early Life Seizures



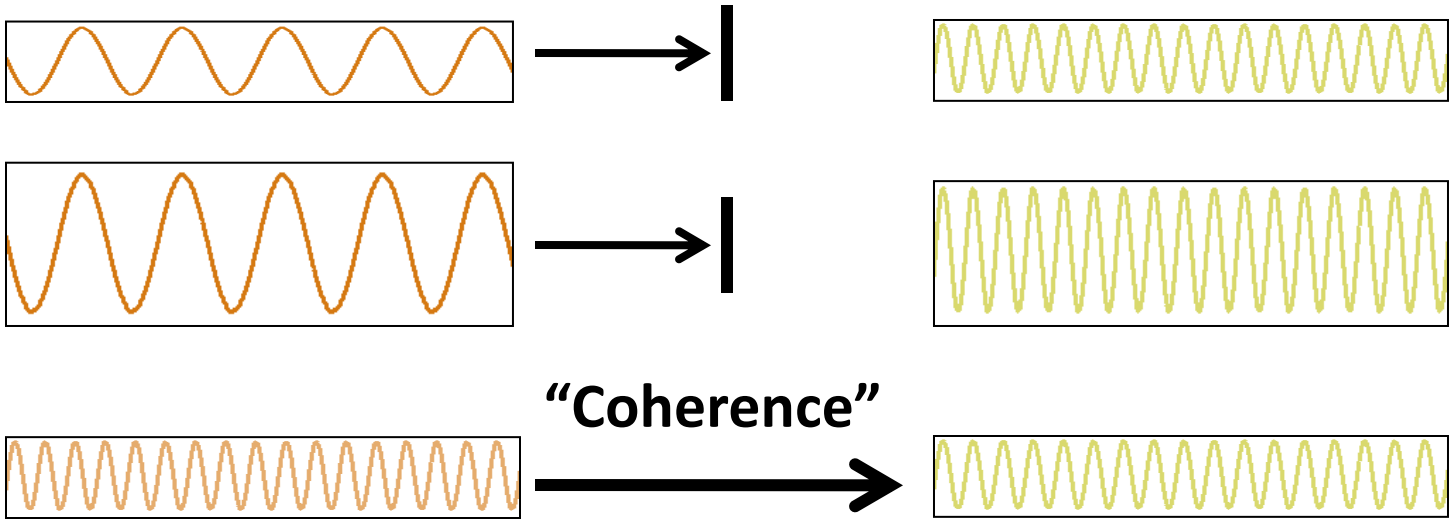

Control Rat
Seizure Rat
Sample
Nosepoke
Match
Frequency (Hz)
10
9
8
7
6
5
-2
-1.5
-1
-0.5
0
0.5
1
1.5
2
Seconds from Event
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0

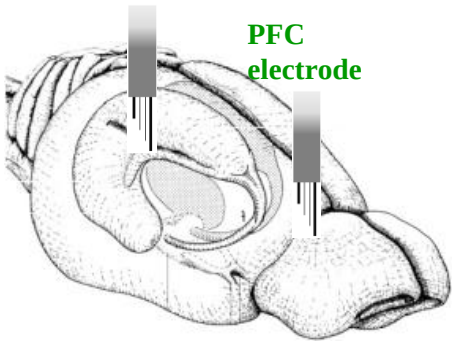
Different areas = different signals

How do they communicate?



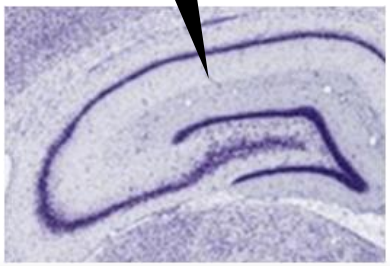
What is Coherence?

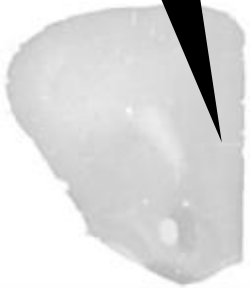


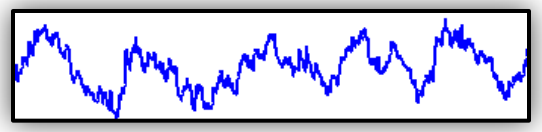


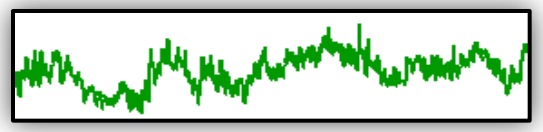
CA1
electrode

PFC
electrode



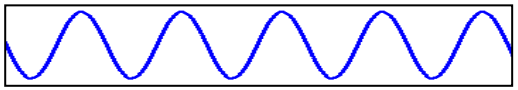




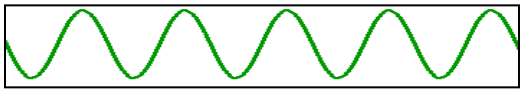


Fourier analysis

Fourier analysis



Memory function



Hippocampal

CA1 CA3

PFC

(Prelimbic)

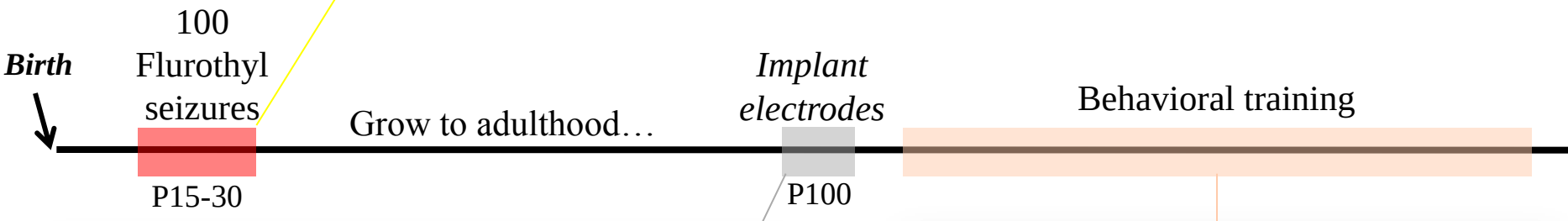
Experiment: Influence of ELS on adult cognition

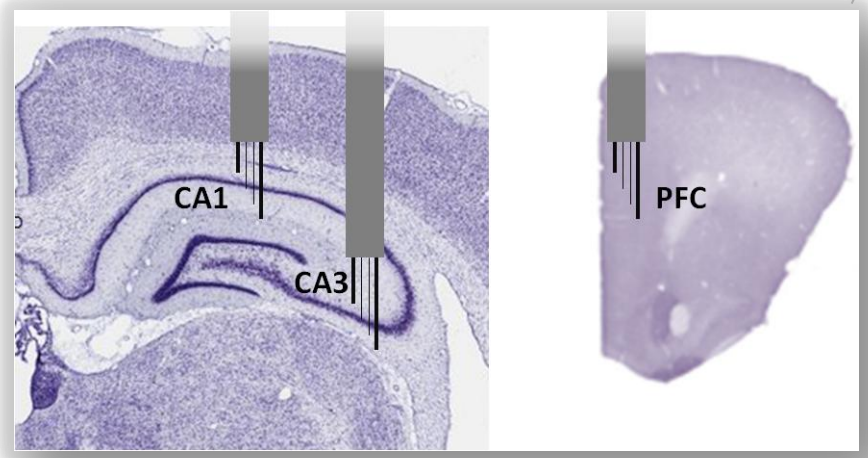
Flurothyl-induced seizures

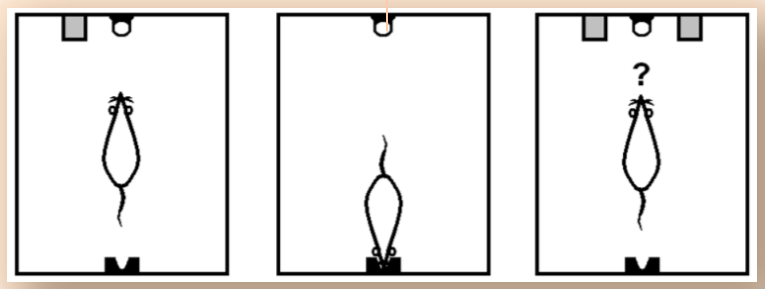
Inhaled chemoconvulsant

- Produces 1-2 minute seizures

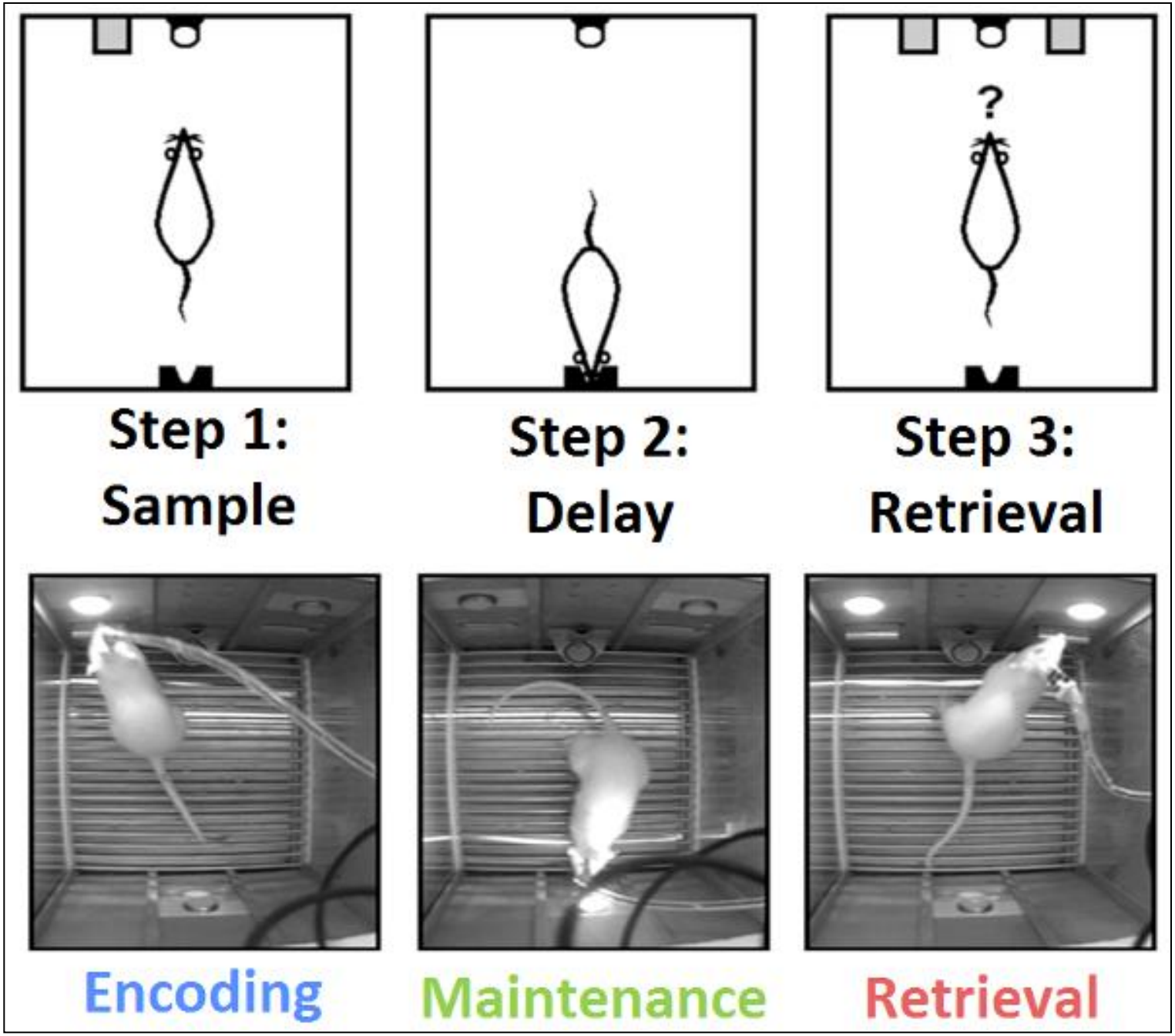
Model of early-life seizures



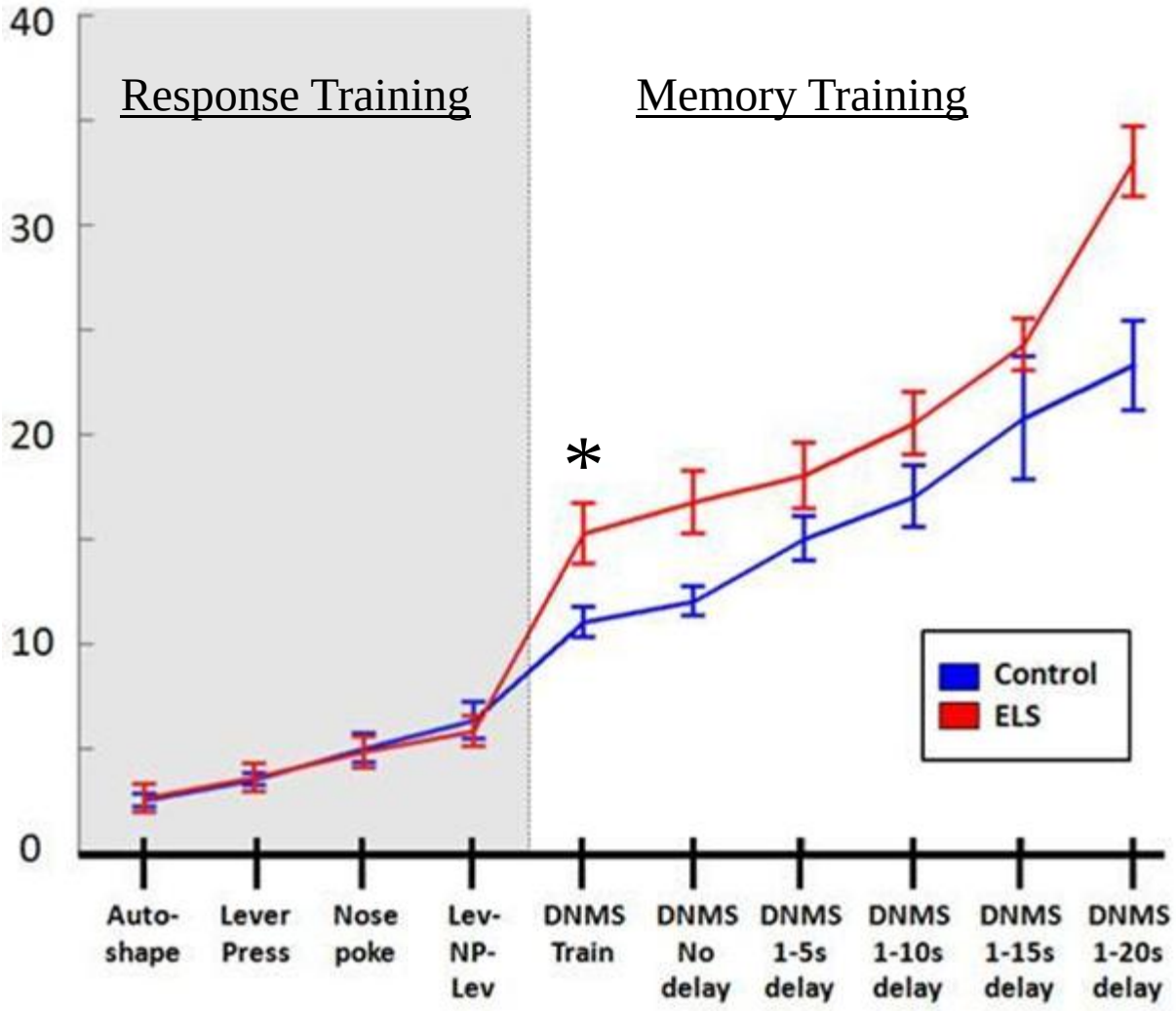




Delayed-Non Match-to-Sample task (DNMS)


?
Step 1:
Sample
Step 2:
Delay
Step 3:
Retrieval
Encoding
Maintenance
Retrieval

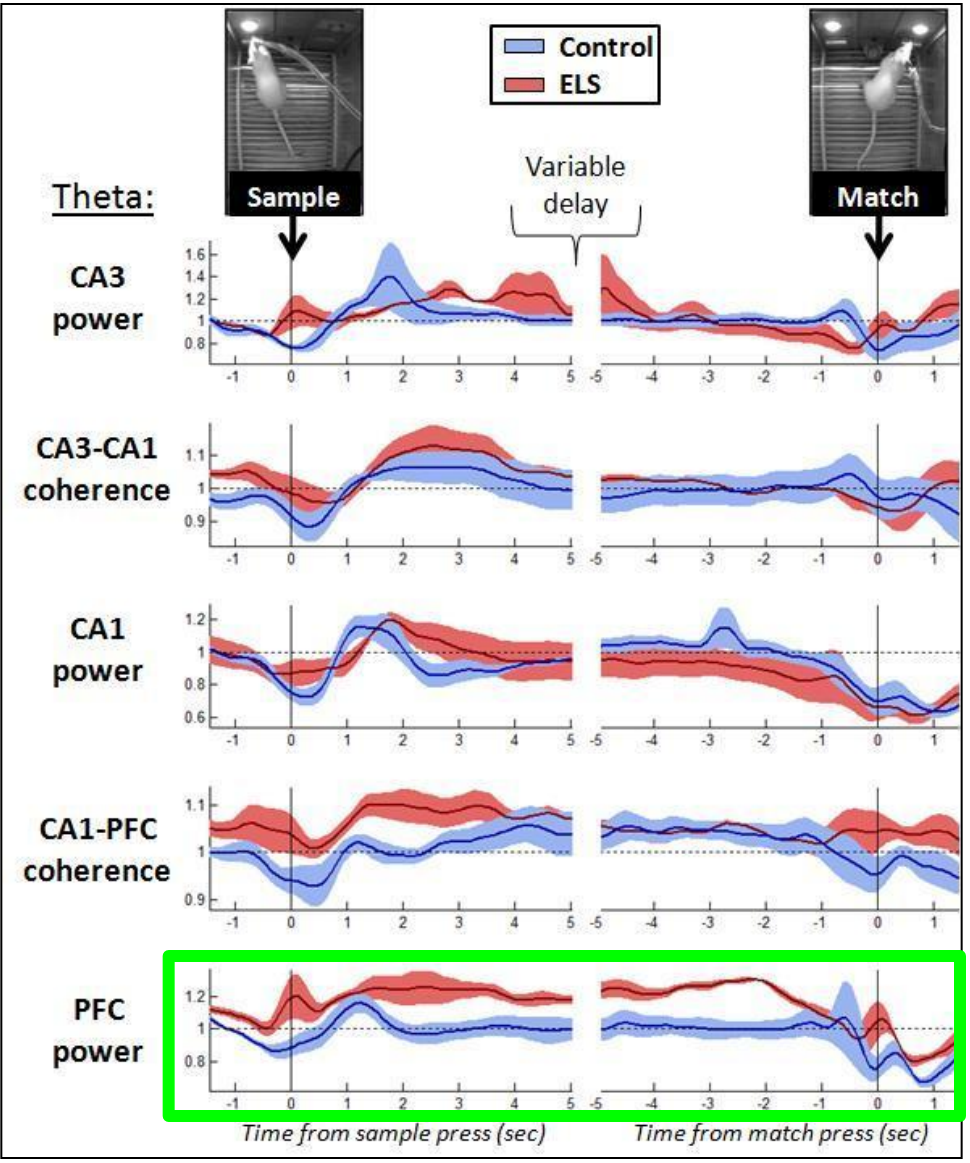
Learning Impairment in DNMS

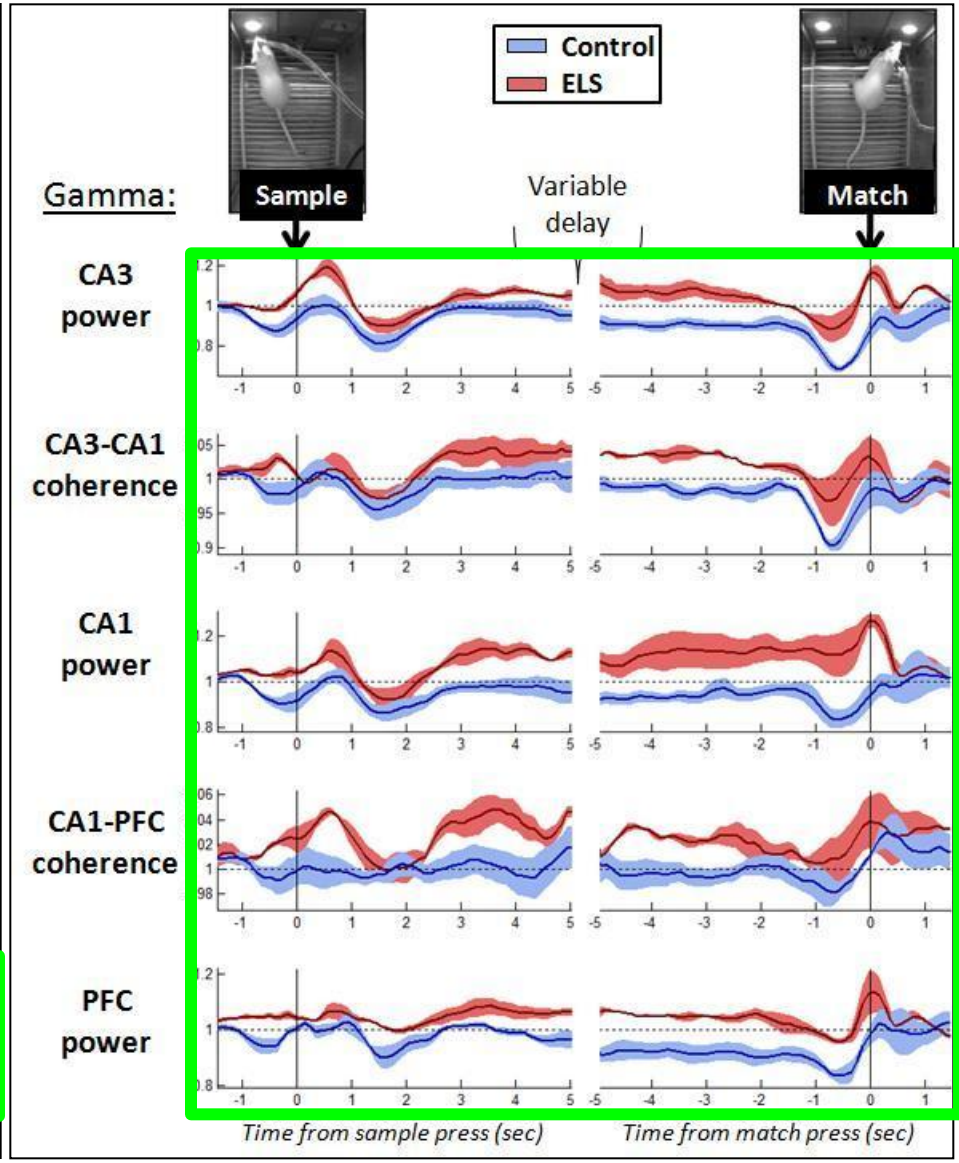


Kleen et al., in preparation

Theta oscillations

Gamma oscillations





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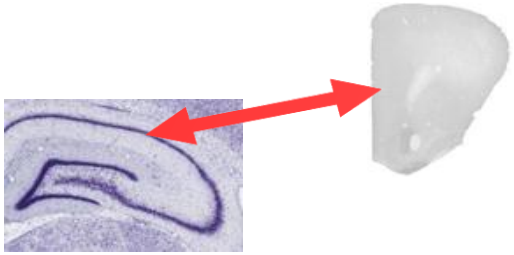
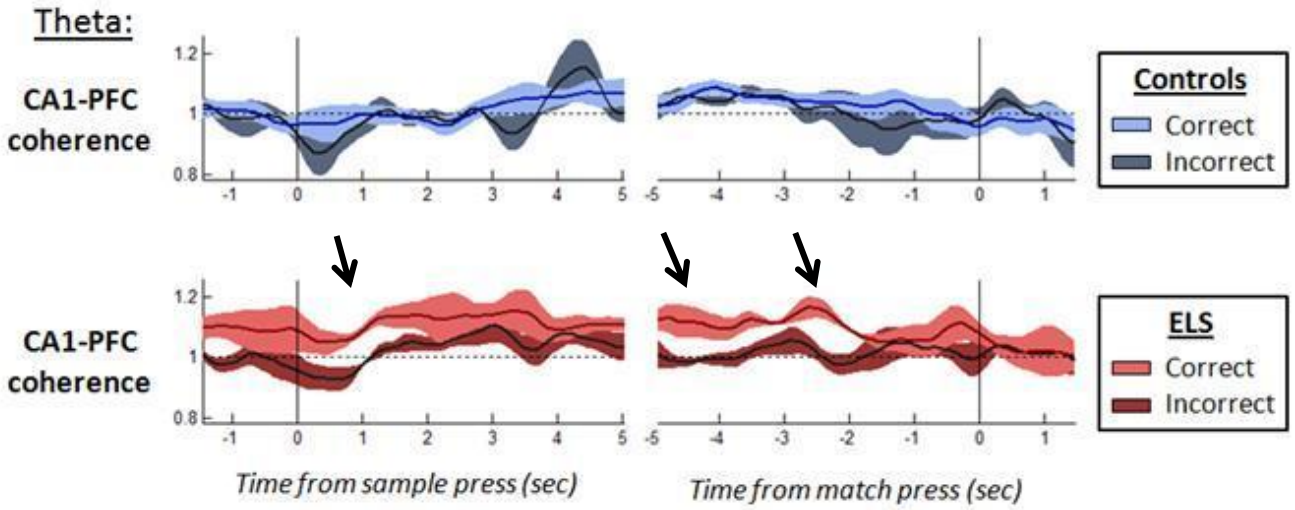
Alternate Theta and Gamma Activity Patterns in the DNMS Task Following ELS



Relation to performance



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Thank You!