EEG IN THE PRETERM INFANT: WINDOWS ON NEURONAL CONNECTIVITY

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SUPPORT AND DISCLOSURES TO DECLARE

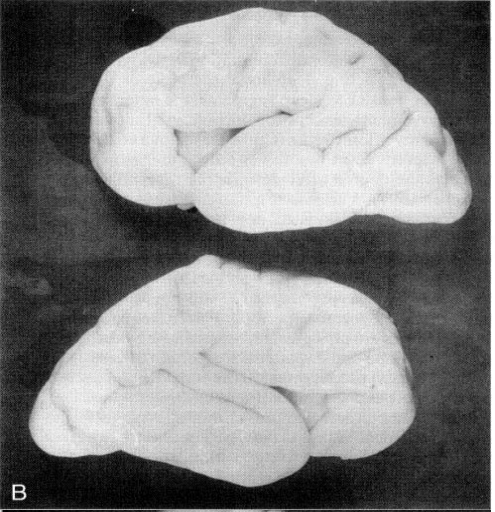
- AA 06390 and DA 03874 (P.I. N. Day)
- NS01110, NS34508, NS0267903, RR 00084, HL 07193 (P.I. M. Scher)
- NR 04926, NR 09814, NR 08587, NR 01894 (co-PIs- S. Ludington, D. Holdich-Davis, M. Scher)

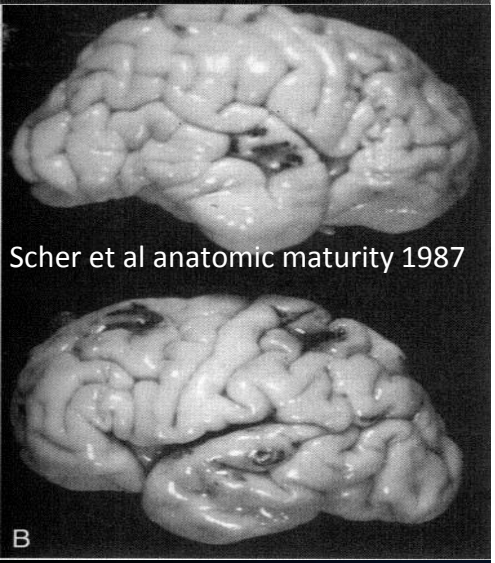
- No Commercial Disclosures

Fetal/Neonatal Neurology Program
EEG-SLEEP Contribution

- State Organization and Maturation
  - Cerebral/Non-cerebral Behaviors
  - Visual + Computer Analyses
- Consider Developmental Origins Theory
- Neuroinformatics with Life-Course Perspective
- Relevance to Diagnosis, Treatment and Outcome


26 wk 3 day
30 wk 5 day
30 wk 9 day
26wk 3D/0
30wk 5D/0
30wk 9D/0
FP3-T3
T3-O1
FP4-T4
T4-O2
FP3-C3
C3-O1
FP4-C4
C4-O2
T3-C3
C3-CZ
CZ-C4
C4-T4
FZ-CZ
CZ-PZ
T3-CZ
T4-CZ
EMG CHIN
LOC1A1
ROC2A2
OC = OUTER CANTHUS
HEAD ON LEFT
HEAD ON RIGHT
EC
ON VENTILATOR
RESP.
EKG.
50 µV
2 sec
A





Scher et al anatomic maturity 1987

Principal component analyses of EEG and 5 sonographic measures

A. Eigenvalues of the correlation matrix

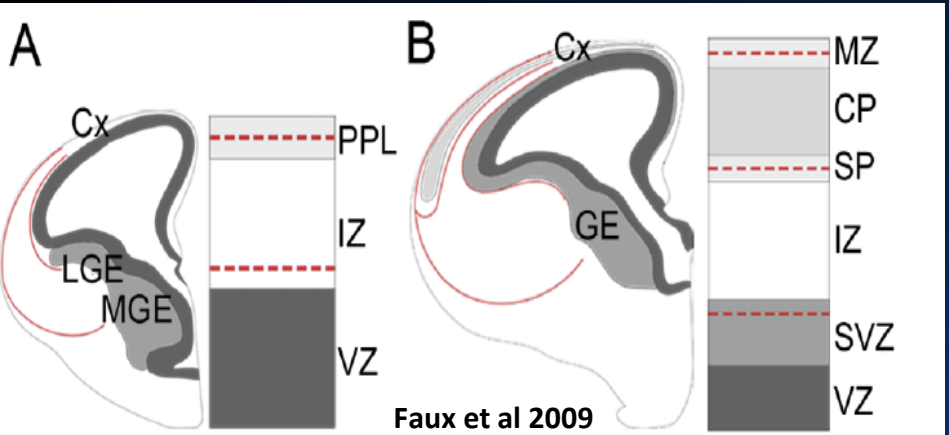
	Eigenvalue	Difference	Proportion	Cumulative
Prin 1	4.34168	3.98298	0.868337	0.86834
Prin 2	0.35870	0.19378	0.071740	0.94008
Prin 3	0.16492	0.06553	0.032984	0.97306
Prin 4	0.09939	0.06408	0.019877	0.99294
Prin 5	0.03531	0.0	0.007062	1.00000

B. Eigenvectors

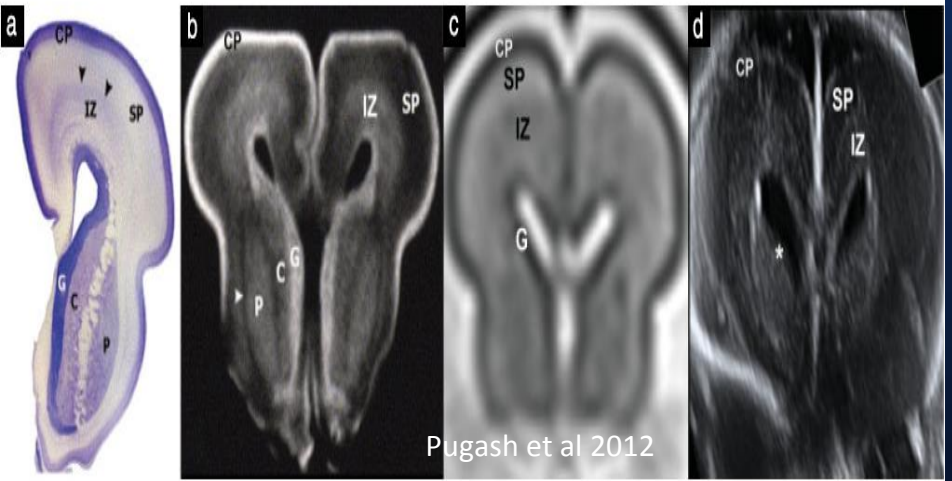
	Prin 1	Prin 2
Head	0.460774	−0.003300
Biparietal	0.461883	−0.357913
Transcerebellar	0.441710	−0.566537
Femur	0.447322	0.283215
Abdominal	0.423258	0.686085

Scher et al sonographic maturity 1994

Maturation of Transient Fetal Brain Structures Affected by Prematurity



Faux et al 2009

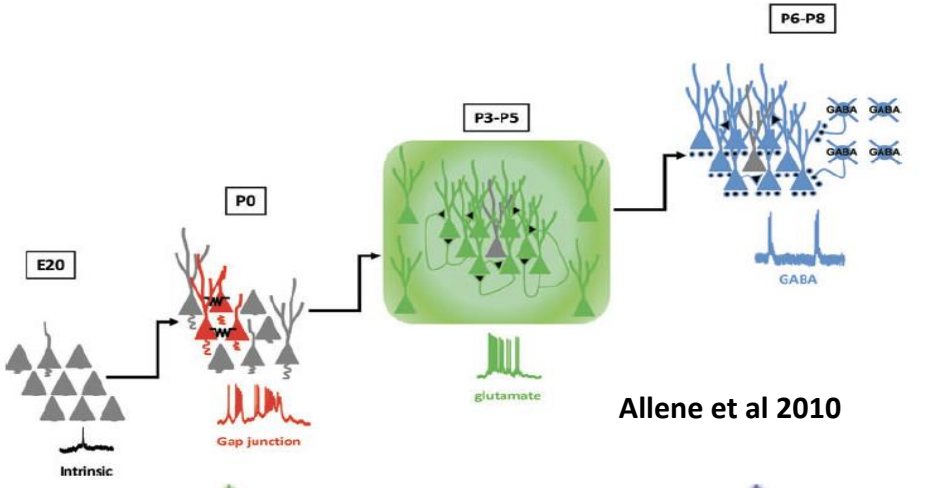


Pugash et al 2012

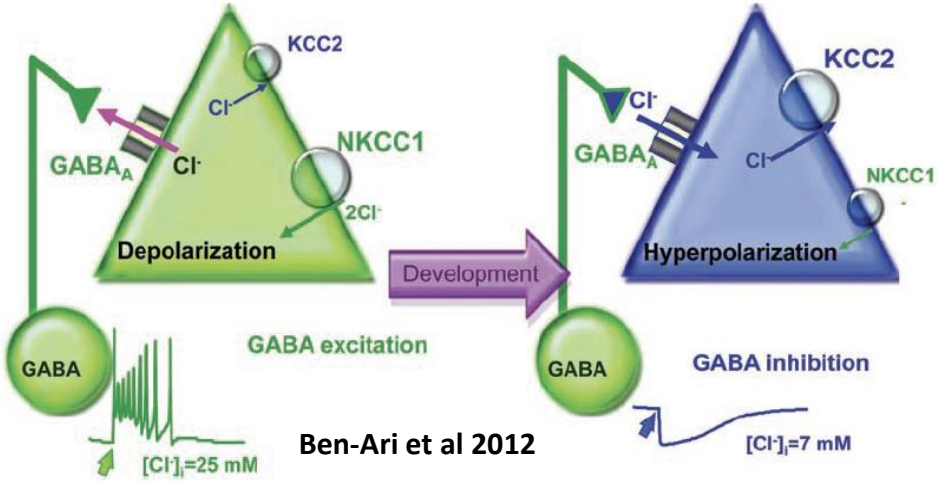
- Children's brain development benefits from longer in utero gestation-Davis et al 2011
- Neurogenesis Continues in the Third Trimester of Pregnancy-Suppressed by Premature Birth- Malik et al 2013
- Early lamination compartments such as the GE and SP affected by prematurity (i.e. interneurons, cortical neurons)
- Pre-oligodentrocyte Maturation Contributes to Myelination Failure in Premature Infants- Buser et al 2012
- From early stress to 12-month development in very preterm infants: Preliminary findings on epigenetic mechanisms and brain growth Fumagalli et al 2018
- Disruption of Interneuron Neurogenesis in Premature Newborns and Reversal with Estrogen Treatment-Tibrewal et al 2018

Maturation of Neurophysiologic Patterns Affected by Prematurity

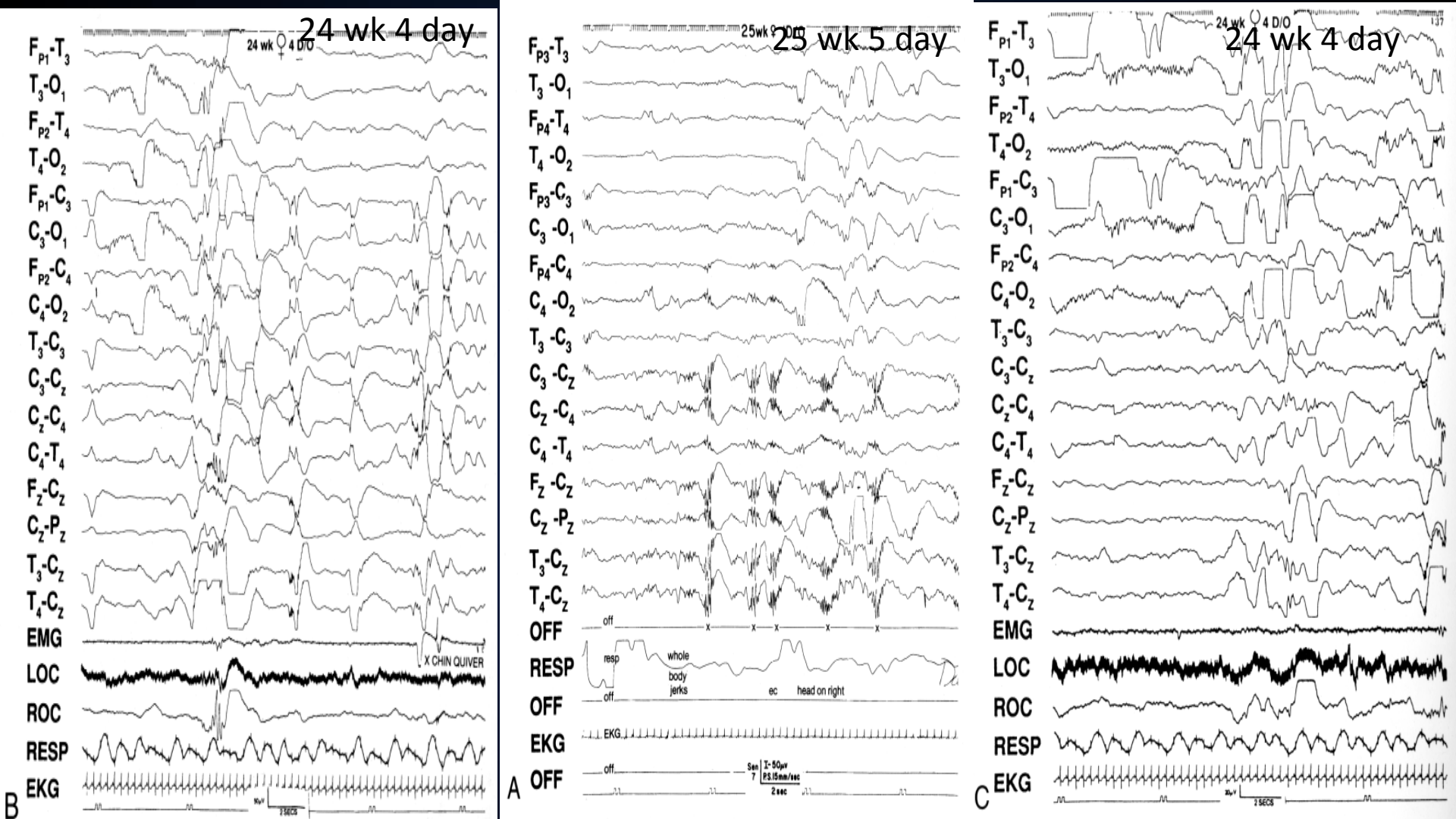
- Mechanisms responsible for synchronization of neuronal activity affected by prematurity
  - Embryonic uncorrelated activities of single neuronal discharges (calcium-driven)
  - Weakly coordinated pre-synaptic multi-neuronal discharges (SPAs)-electrical coupling by gap junctions
  - Large-scale coherent discharges by synaptic activities: cENOs (glutamatergic bursts) followed by GDPs (GABAergic bursts)
  - Region-specific network oscillations from thalamocotical connections generating specific neuronal discharge sequences
- Molecular alterations by prematurity at the neuronal membrane affecting neurotransmitter functions such as the two chloride co-transporters NKCC1 and KCC2 involved in the shift in GABA from excitatory to inhibitory with brain maturation

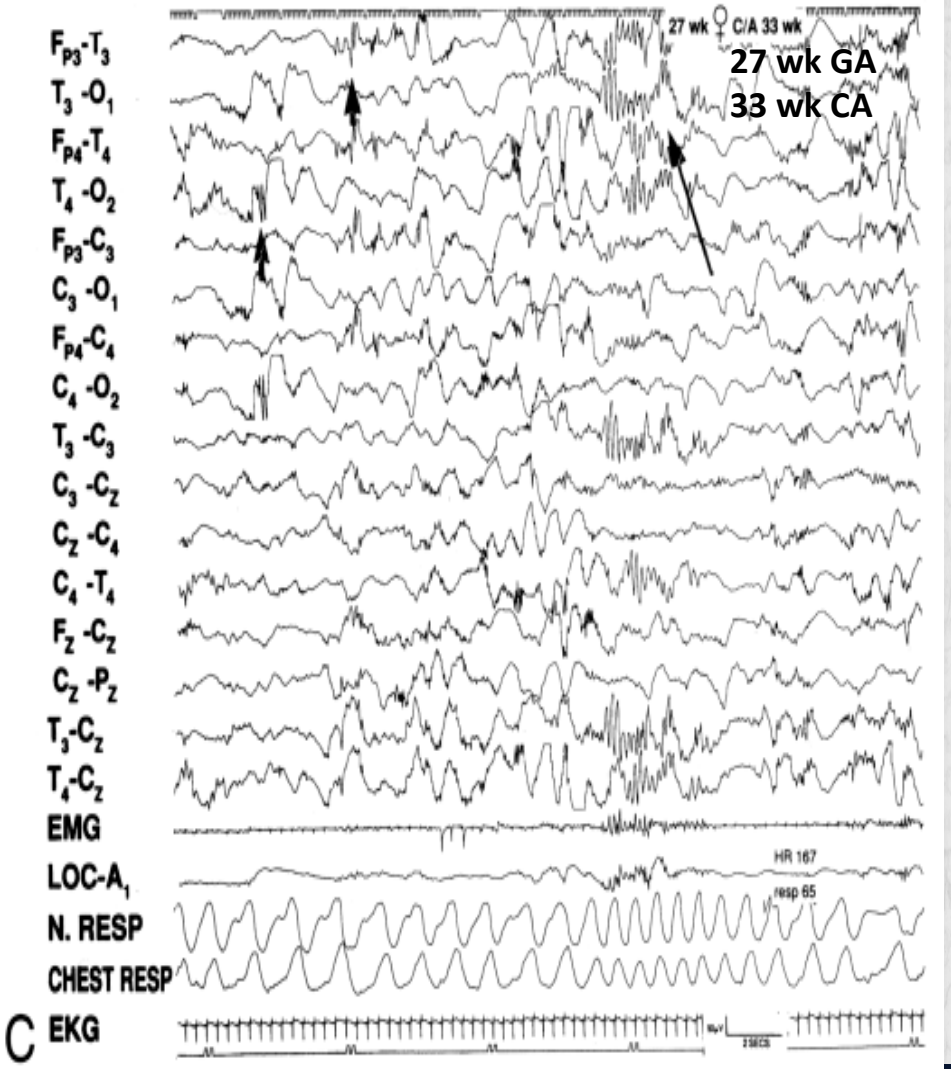


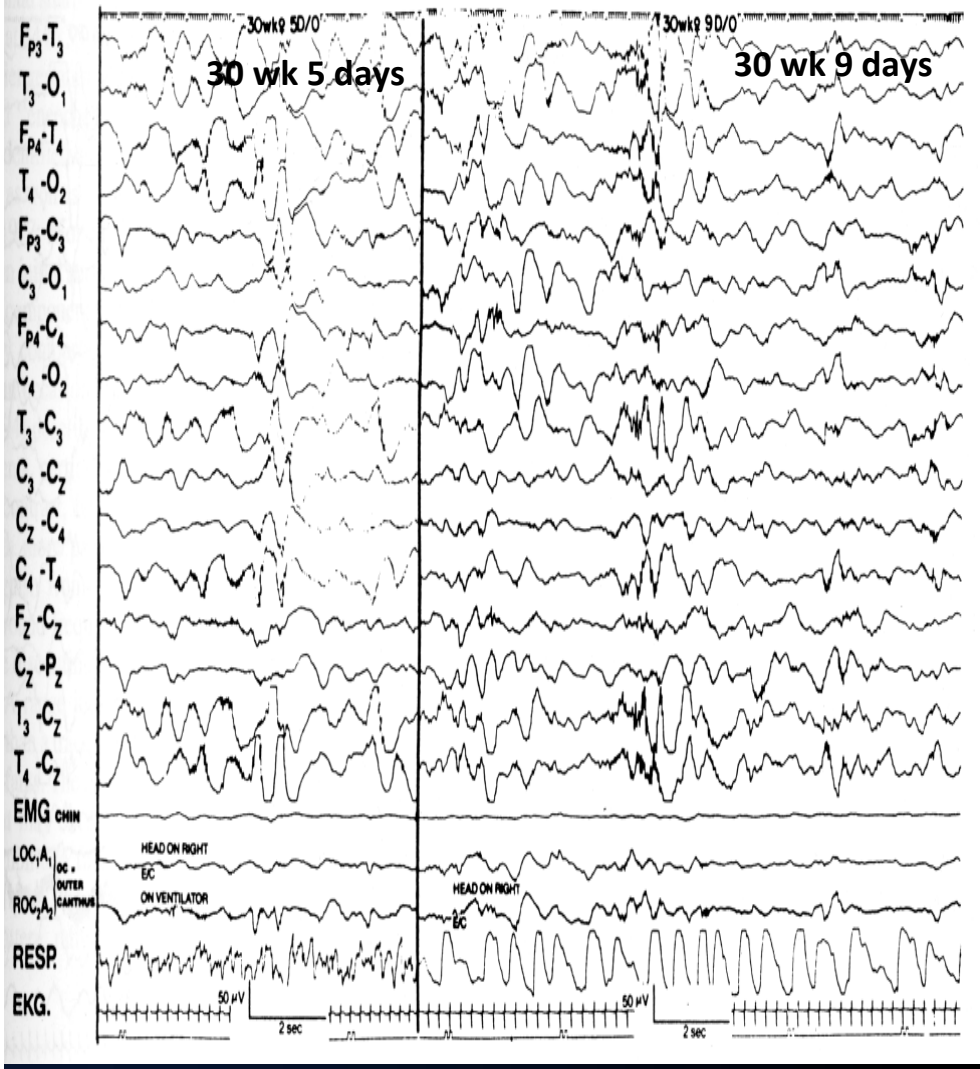
Allene et al 2010



Ben-Ari et al 2012


24 wk 4 day
25 wk 5 day
24 wk 4 day
24 wk 4 D/O
25wk
24 wk 4 D/O
F_{P1}-T_3
T_3-O_1
F_{P2}-T_4
T_4-O_2
F_{P1}-C_3
C_3-O_1
F_{P2}-C_4
C_4-O_2
T_3-C_3
C_3-C_z
C_z-C_4
C_4-T_4
F_z-C_z
C_z-P_z
T_3-C_z
T_4-C_z
EMG
LOC
ROC
RESP
EKG
X CHIN QUIVER
F_{P3}-T_3
F_{P4}-T_4
F_{P3}-C_3
F_{P4}-C_4
OFF
RESP
resp
whole
body
jerks
ec
head on right
EKG
A
B
C
2 SECS

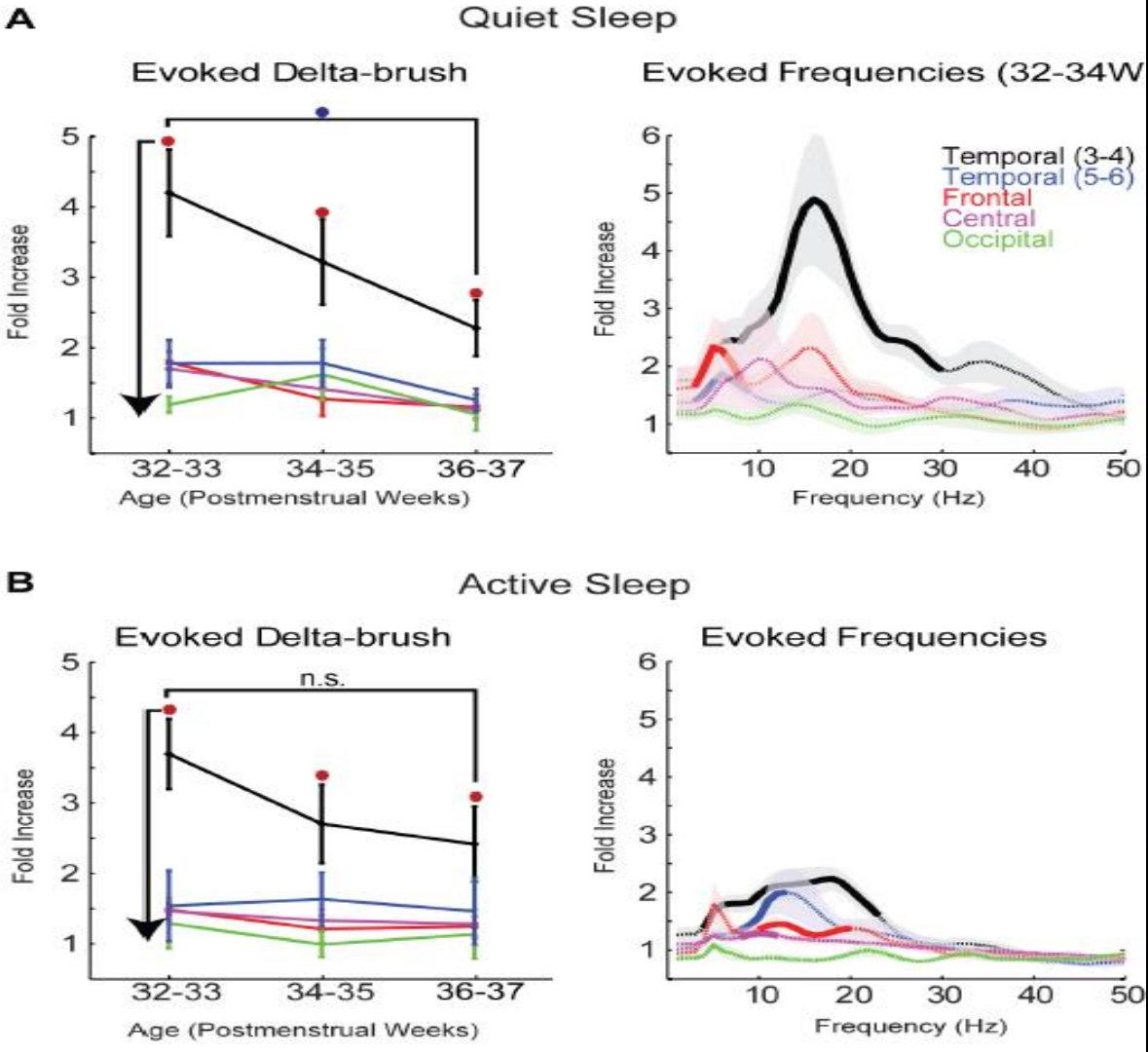

27 wk ♀ C/A 33 wk
27 wk GA
33 wk CA
FP3-T3
T3-O1
FP4-T4
T4-O2
FP3-C3
C3-O1
FP4-C4
C4-O2
T3-C3
C3-CZ
CZ-C4
C4-T4
FZ-CZ
CZ-PZ
T3-CZ
T4-CZ
EMG
HR 167
LOC-A1
resp 65
N. RESP
CHEST RESP
EKG
2 SECS

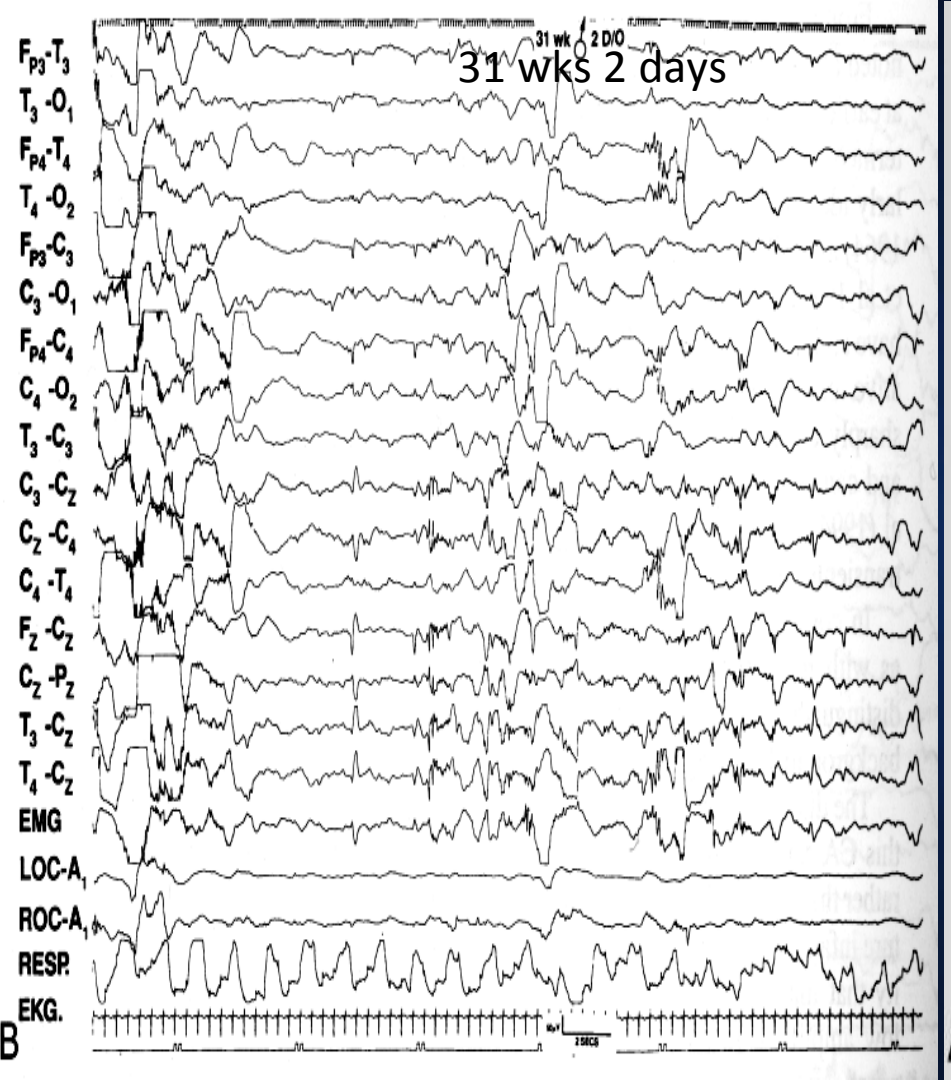

30wk9 5D/0
30wk9 9D/0
30 wk 5 days
30 wk 9 days
FP3-T3
T3-O1
FP4-T4
T4-O2
FP3-C3
C3-O1
FP4-C4
C4-O2
T3-C3
C3-CZ
CZ-C4
C4-T4
FZ-CZ
CZ-PZ
T3-CZ
T4-CZ
EMG CHIN
LOC1A1
ROC2A2
OC = OUTER CANTHUS
HEAD ON RIGHT
EC
ON VENTILATOR
HEAD ON RIGHT
EC
RESP.
EKG.
50 µV
2 sec
50 µV
2 sec

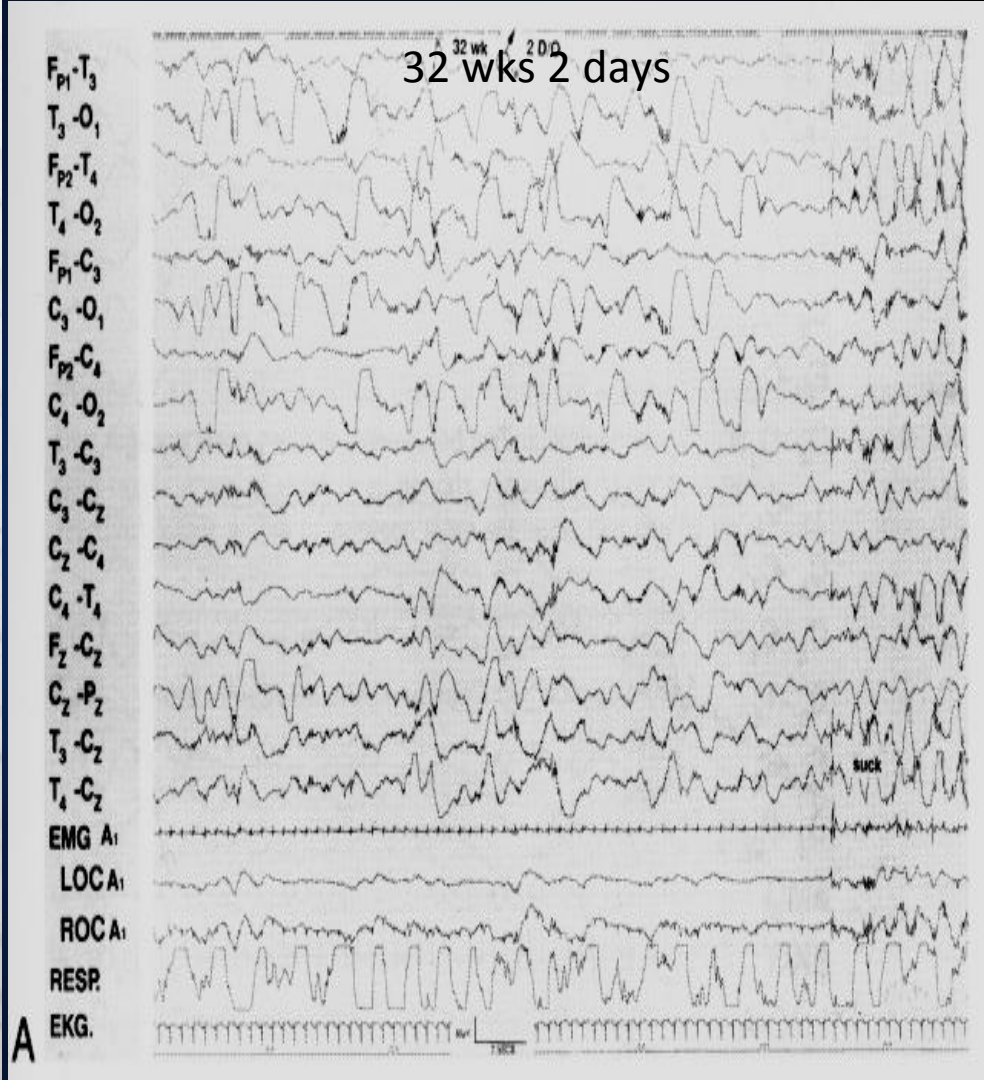
Delta brushes evoked by auditory stimuli
thalamo-cortical pathways
sensory-driven
subplate -cortical mantle connections
Chipaux et al 2013

temporal theta endogenous cortical rhythms
not sensory driven
Routier et al 2017

physiologic asynchrony
developing intra/interhemispheric connectivity using ASI
Koolen et al 2016



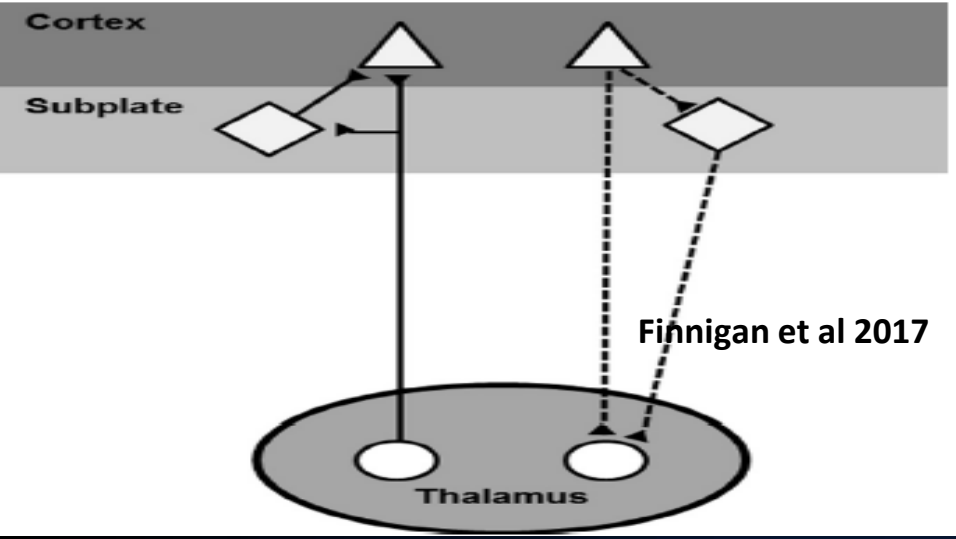

31 wk 2 D/O
31 wks 2 days
FP3-T3
T3-O1
FP4-T4
T4-O2
FP3-C3
C3-O1
FP4-C4
C4-O2
T3-C3
C3-CZ
CZ-C4
C4-T4
FZ-CZ
CZ-PZ
T3-CZ
T4-CZ
EMG
LOC-A1
ROC-A1
RESP.
EKG.
B


32 wk 2 D/O
32 wks 2 days
FP1-T3
T3-O1
FP2-T4
T4-O2
FP1-C3
C3-O1
FP2-C4
C4-O2
T3-C3
C3-CZ
CZ-C4
C4-T4
FZ-CZ
CZ-PZ
T3-CZ
T4-CZ
suck
EMG A1
LOC A1
ROC A1
RESP.
EKG.
A

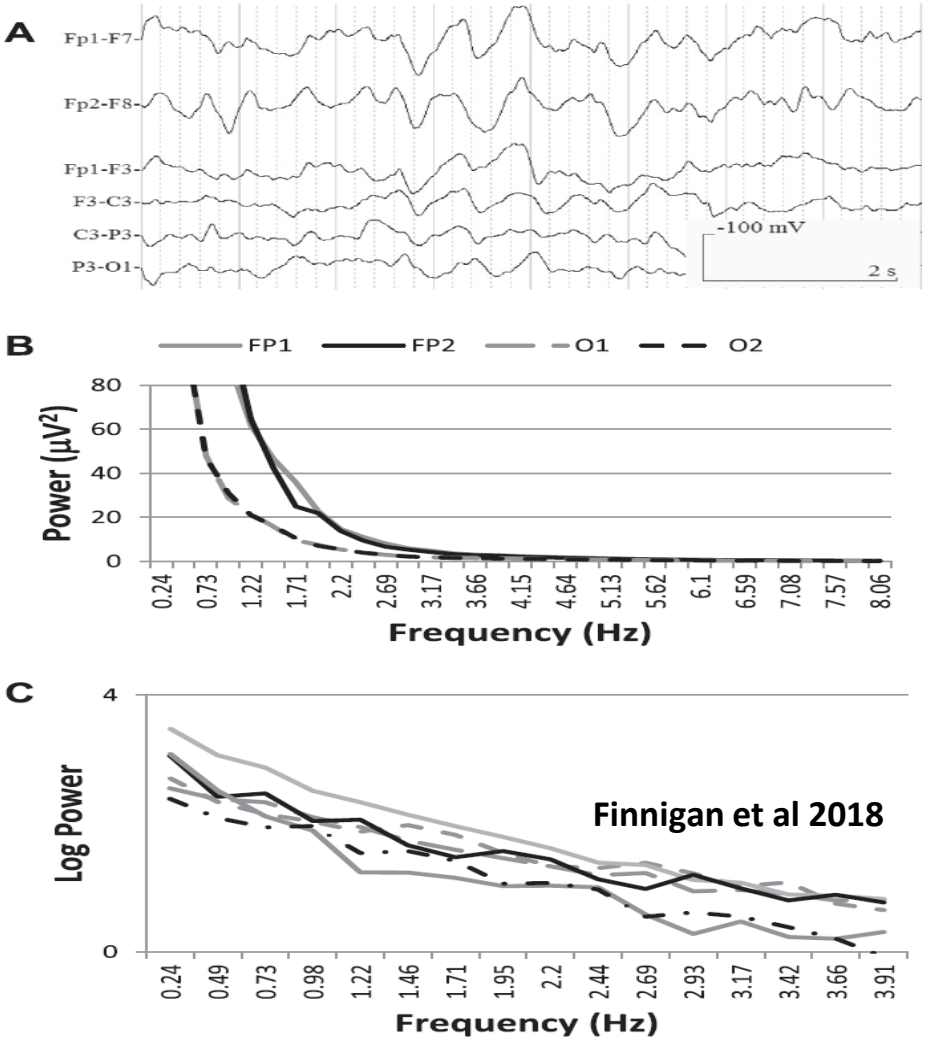
Delta rhythms- gestational age/region specific
<28 wks- central/vertex
>28 wks- temporal/occipital

Higher amplitudes frontal than occipital
several peaks of delta spectral power (0.5-3.5 Hz)

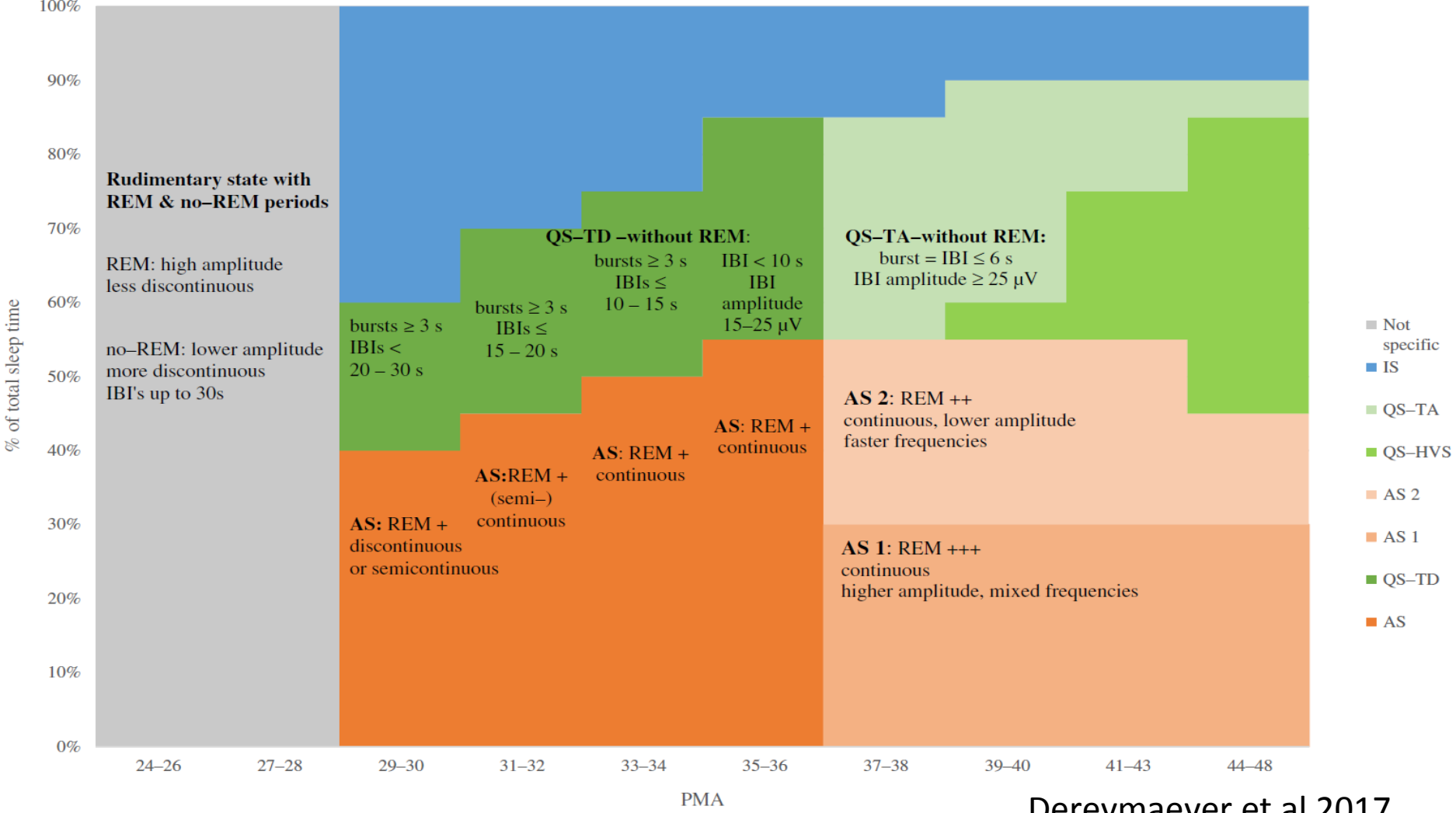
Clinical correlations
transient thalamo-cortical dysrhythmia
Combine visual and digital analyses
Correlate with advanced neuroimaging



Finnigan et al 2017



Finnigan et al 2018



Dereymaeyer et al 2017

Full-term sleep cycle average ± 50–60 min.

BRAC for preterm

Interfeeding 40-50 min

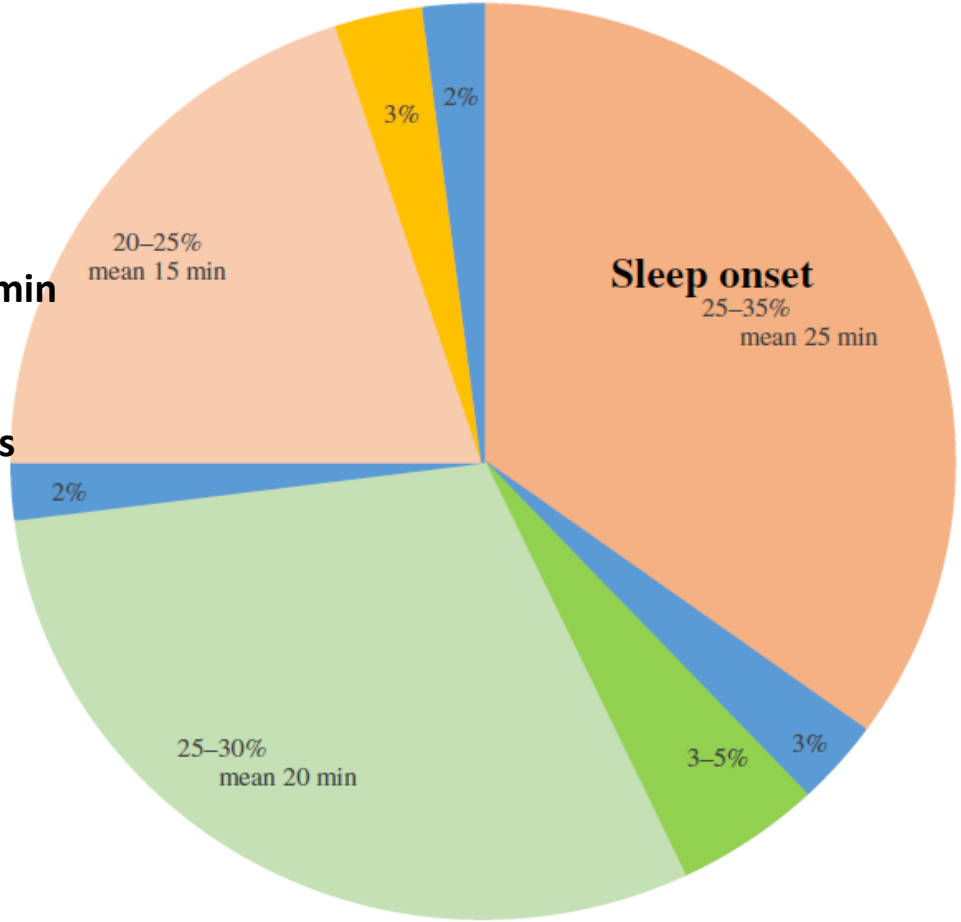
Sleep Cycle by term

30-70 min

Diurnal/Circadian rhythms effect weak

Maternal/placental generator in-utero

Ultradian rhthyms predominant for the neonate

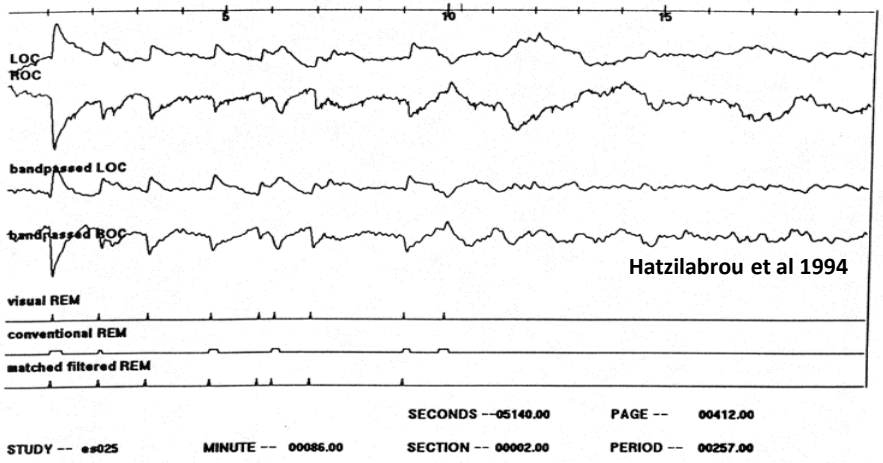


AS 1 IS QS–HVS QS–TA AS 2 W

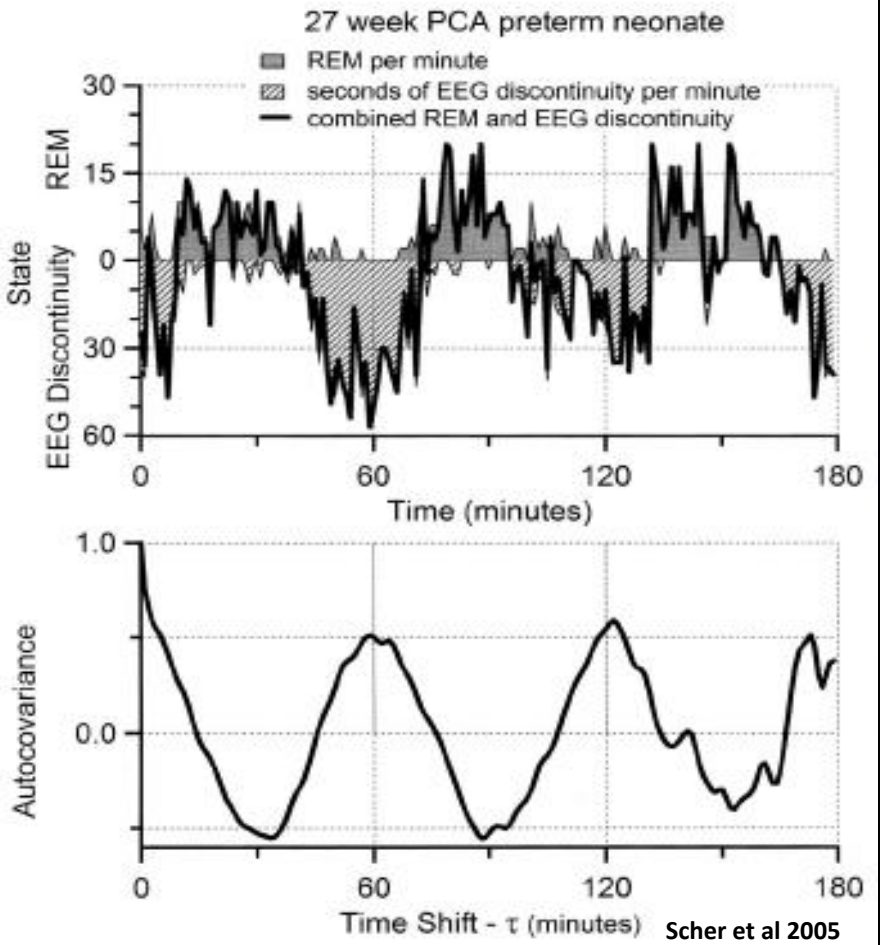
Dereymaeker et al 2017

REMS

- Present at PT GA and in fetus
  small corneo-retinal potential
- Concordance with continuous EEG
  beginning in extreme PT<28 wks
- Reciprocity with discontinuous sleep
- 1 hour cyclicity 23-40 weeks



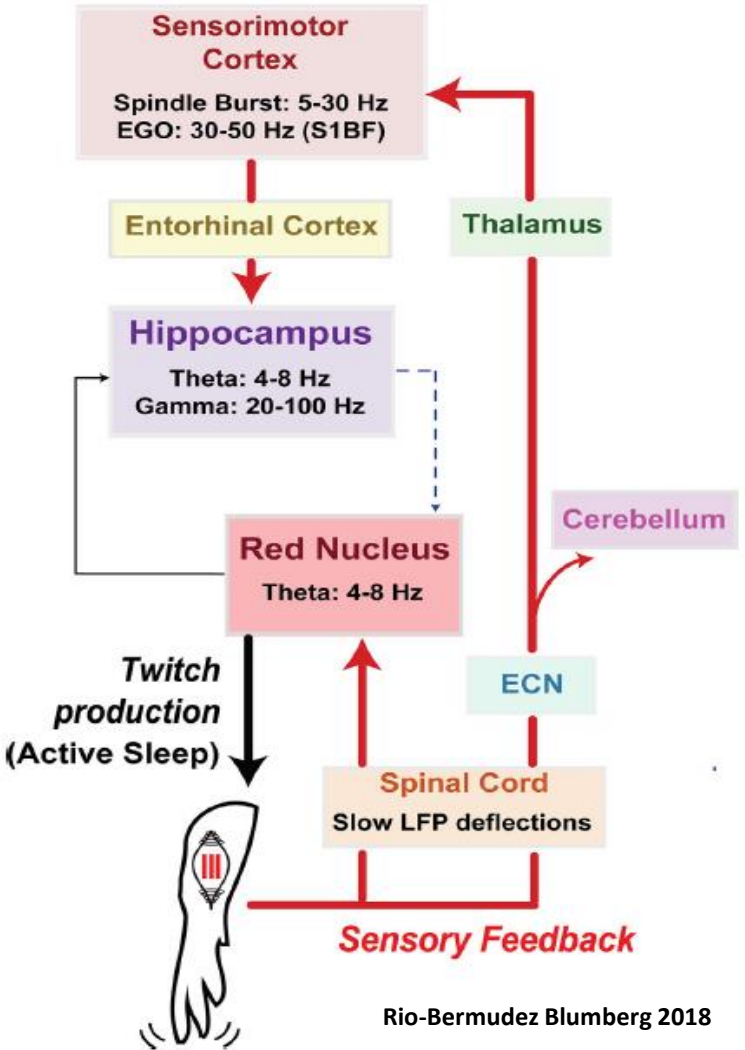
Hatzilabrou et al 1994



Scher et al 2005

Motility Patterns

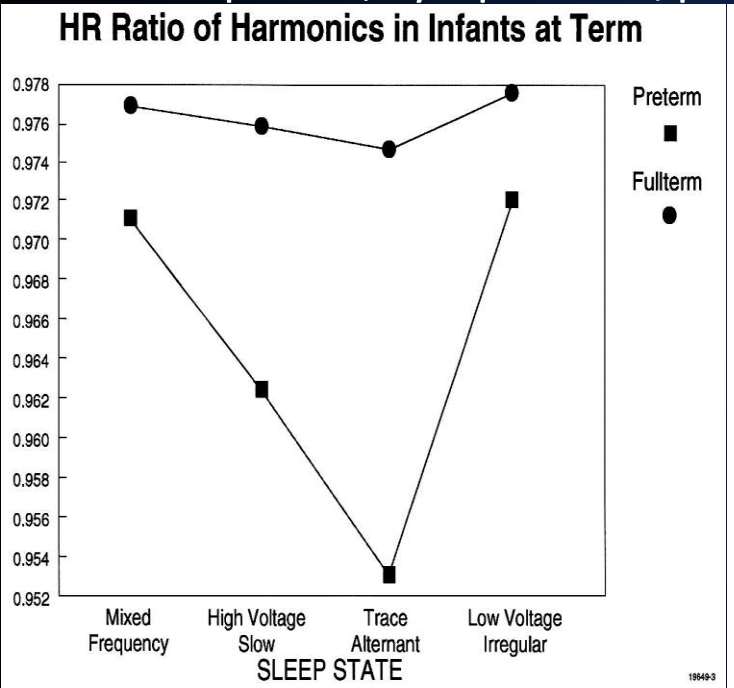
- Fetal movements 10 weeks post-conception
- Quantity/quality and #/unit/time decrease with maturation
  - 17% at 24 weeks , 7% at 40 weeks
  - Myoclonic, whole body -preterm
  - Segmental smaller –term
- State-regulated movements <30 wks- active sleep
- Precisely timed sensory feedback from movements
  - Repeated activity promote synchronization of different oscillatory activities throughout neuroaxis
  - Promotes neuroplasticity (adaptive/maladaptive)
- Coupling of somatic and cardiac activity with increasing GA
  - RMMs (begin at 32 weeks strong by 38 weeks)

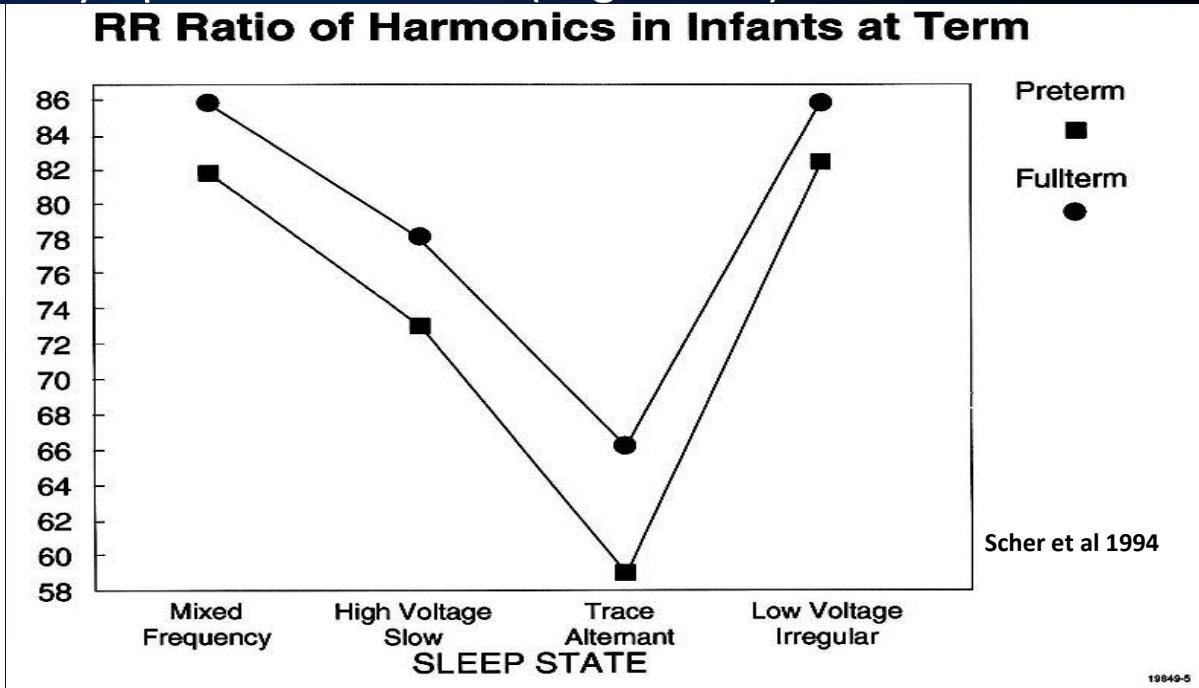


Rio-Bermudez Blumberg 2018

Cardiorespiratory Behaviors

- Periodic breathing/respiratory pauses more prevalent in preterms
- Slower rates during QS than AS
- Decreased variability during QS-more prominent with maturation
- HRV Spectra; sympathetic/parasympathetic balance (vagal tone)

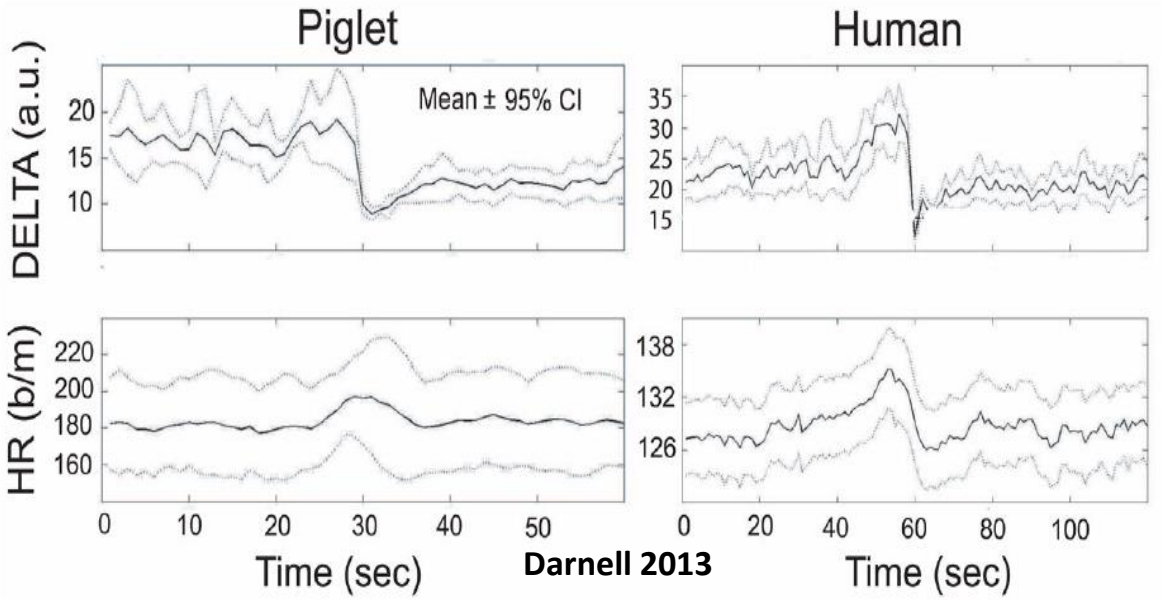




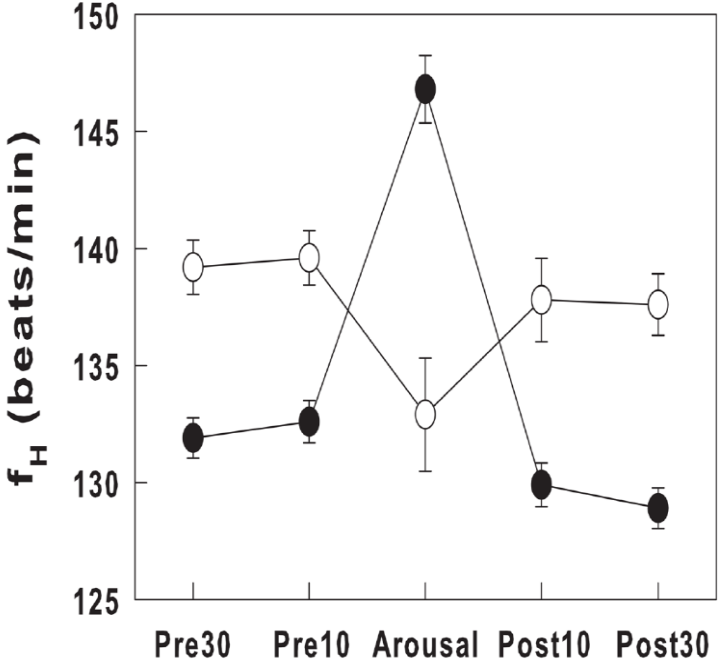
Scher et al 1994

Ontogeny of Arousals

- State Regulation-sleep transition/waking promoter-protective response
- Cortical vs. sub-cortical types of arousal-promote neuroplasticity
- Decrease in number/duration with sleep cycle maturation-with>QS expression



Darnell 2013



Active Sleep/REM - 26 week GA Premie @ 34 weeks PMA (EEG-2-619-0057)

30 sec | 20 uV | neo.mtg | 0.3 sec | 70Hz | 60Hz

Fp1-T3
T3-O1
Fp2-T4
T4-O2
Fp1-C3
C3-O1
Fp2-C4
C4-O2
T3-C3
C3-Cz
Cz-C4
C4-T4
Fz-Cz
Cz-Pz
T3-Cz
T4-Cz
LOC
ROC
Chin
Rib
Abd
EkgLR
HR
SaO2

Comments: REM, REM, REM, REM, REM, REM, REM, REM, REM, Continuous, REM, REM, REM

01:19:00

Quiet Sleep/Trace Discontinue - 26 week GA Premie @ 34 weeks PMA (EEG-2-619-0057)

30 sec | 20 uV | neo.mtg | 0.3 sec | 70Hz | 60Hz

Fp1-T3
T3-O1
Fp2-T4
T4-O2
Fp1-C3
C3-O1
Fp2-C4
C4-O2
T3-C3
C3-Cz
Cz-C4
C4-T4
Fz-Cz
Cz-Pz
T3-Cz
T4-Cz
LOC
ROC
Chin
Rib
Abd
EkgLR
HR
SaO2

Comments: interburst, interburst, interburst, Trace Discontinue

0:36:30

Awakening - full-term @ 40 weeks PMA (EEG-2-045-0010)

30 sec | 20 uV | neo.mtg | 0.3 sec | 70Hz | 60Hz

Fp1-T3
T3-O1
Fp2-T4
T4-O2
Fp1-C3
C3-O1
Fp2-C4
C4-O2
T3-C3
C3-Cz
Cz-C4
C4-T4
Fz-Cz
Cz-Pz
T3-Cz
T4-Cz
LOC
ROC
Chin
Rib
Abd
Ekg
HR
SaO2

Comments: Awake, Eyes Open

00:50:00

Trace Alternant Sleep - full-term @ 40 weeks PMA (EEG-2-073-0001)

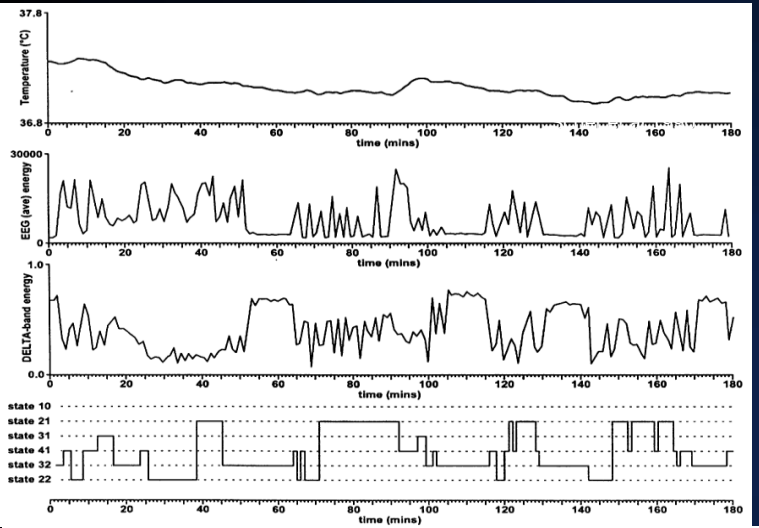
30 sec | 20 uV | neo.mtg | 0.3 sec | 70Hz | 60Hz

Fp1-T3
T3-O1
Fp2-T4
T4-O2
Fp1-C3
C3-O1
Fp2-C4
C4-O2
T3-C3
C3-Cz
Cz-C4
C4-T4
Fz-Cz
Cz-Pz
T3-Cz
T4-Cz
LOC
ROC
Chin
Rib
Abd
Ekg
HR
SaO2

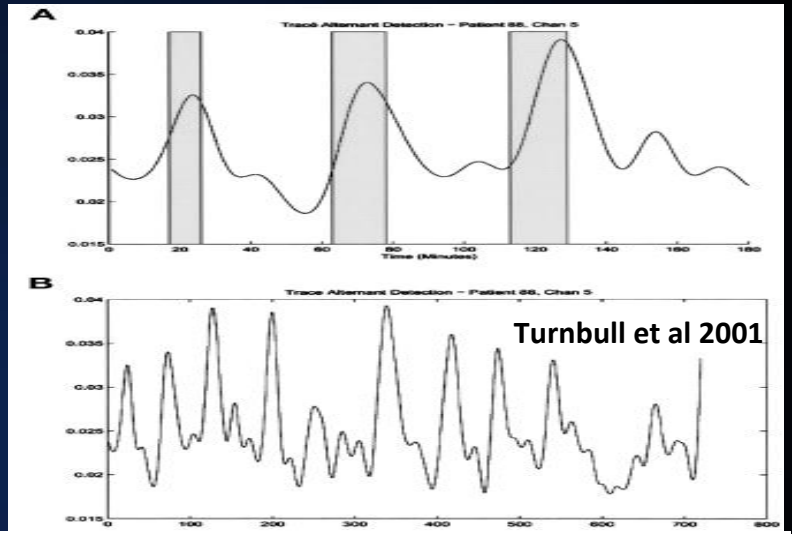
Comments: TA

01:28:00

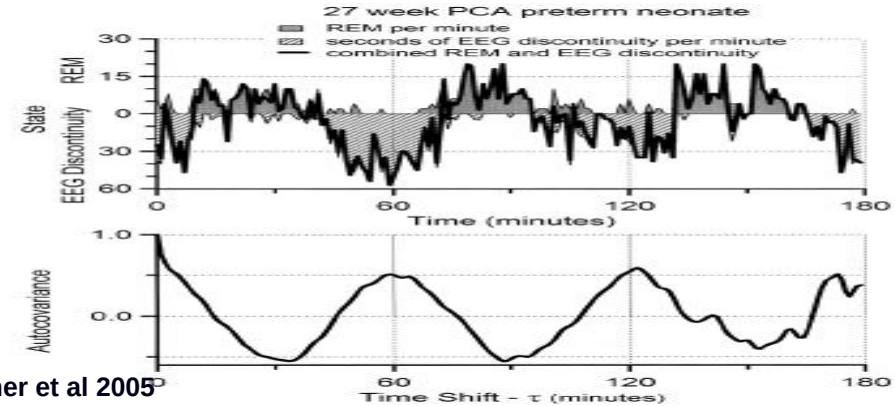
Analytic Strategies to Depict Brain Organization/Maturation



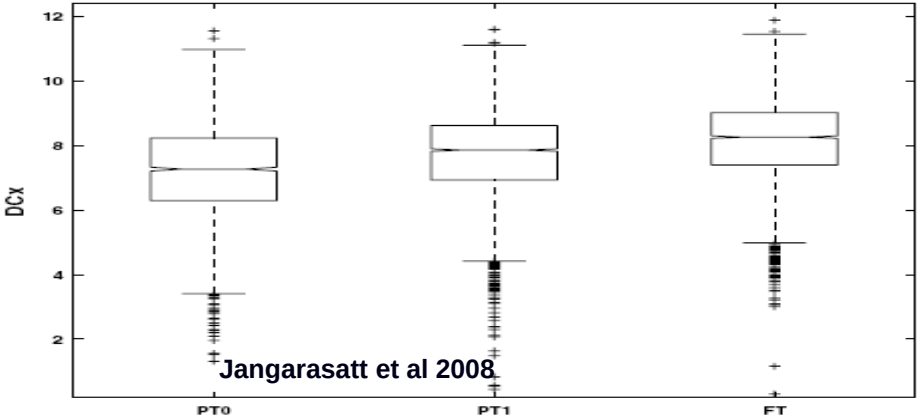
- Visual Analyses
- Digital Analyses
- Linear and non-linear computations to study time series



Turnbull et al 2001



Scher et al 2005



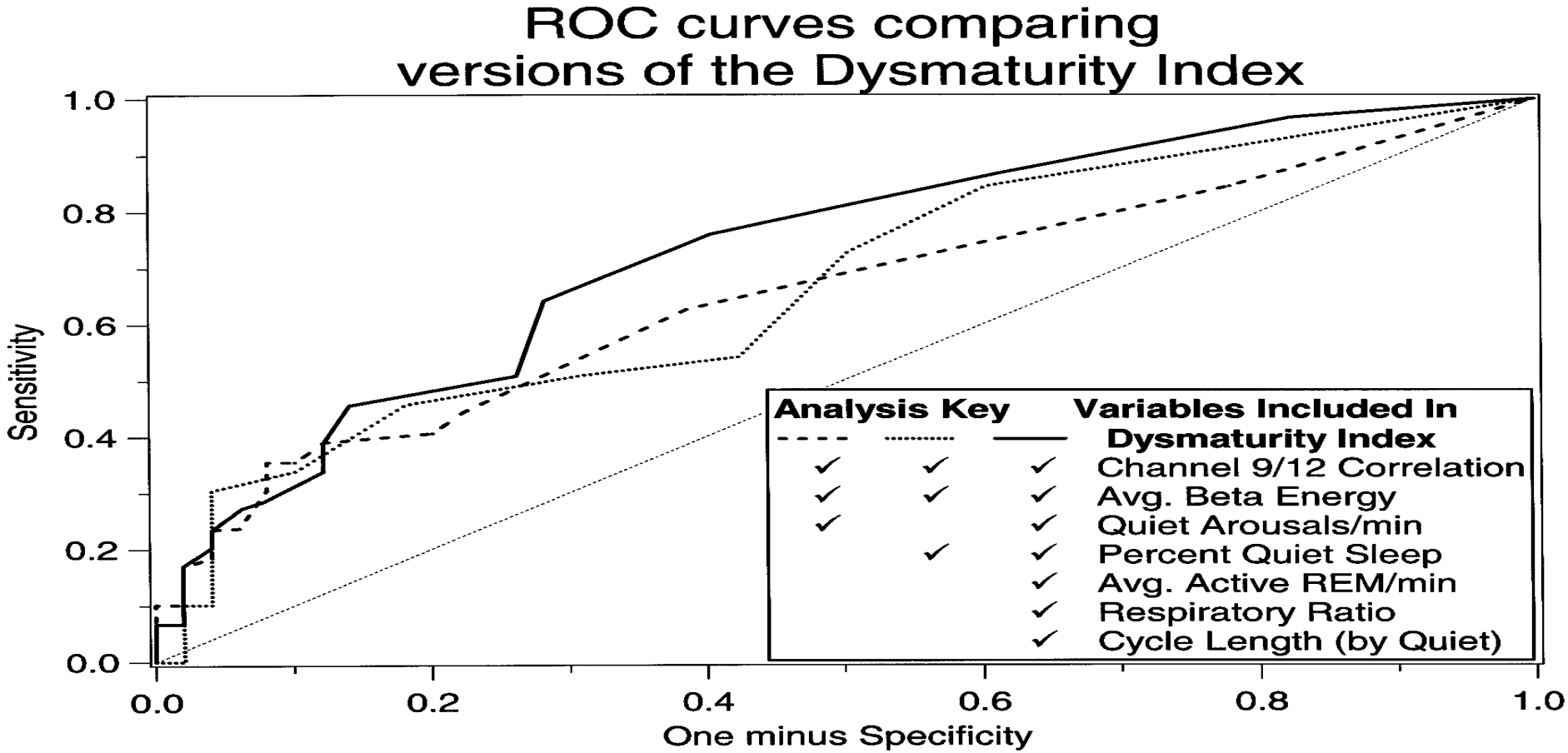
Jangarasatt et al 2008

A Physiologic Dysmaturity Index

Differences in Brain Function between Healthy PT/FT

1. Lower spectral beta EEG energies (delayed?)
2. Higher spectral EEG correlation values (accelerated?)
3. Higher quiet sleep percentages (accelerated?)
4. Fewer arousals (accelerated?)
5. Fewer REMs (accelerated?)
6. Lower respiratory regularity (delayed?)
7. Longer sleep cycle lengths (accelerated?)

- Interconnected neuronal networks altered by conditions of prematurity
  - prenatal/postnatal conditions and/or disease
  - clinical interventions
- Accelerated or delayed specific to physiologic marker-developmental neuroplasticity
- Correlation with other biomarkers-imaging, genetic markers
- Adaptive or maladaptive depending on the age of physiologic expression? -lower neurodevelopmental scores in the healthy preterms at 24 months of age



ROC curve for dysmaturity index, note greater area under the curve for 7 vs. 3 sleep behaviors (Scher et al., 2003)

Longitudinal EEG/Sleep studies: Visual/spectral EEG scores, demographic/clinical histories

Maternal
- 37-year-old, G 7, P now 4, 2-2-3-5
- Maternal pre-eclampsia
- risk - twin gestation
- depression
- Hospitalization
  - (DOL -11 to -8)
  - severe headache
  - incr. blood pressure
  - 2+ proteinuria
- Hospitalization
  - (DOL -4 to +3)
- hypertension, chronic
- med - mag. sulfate secondary to toxemia

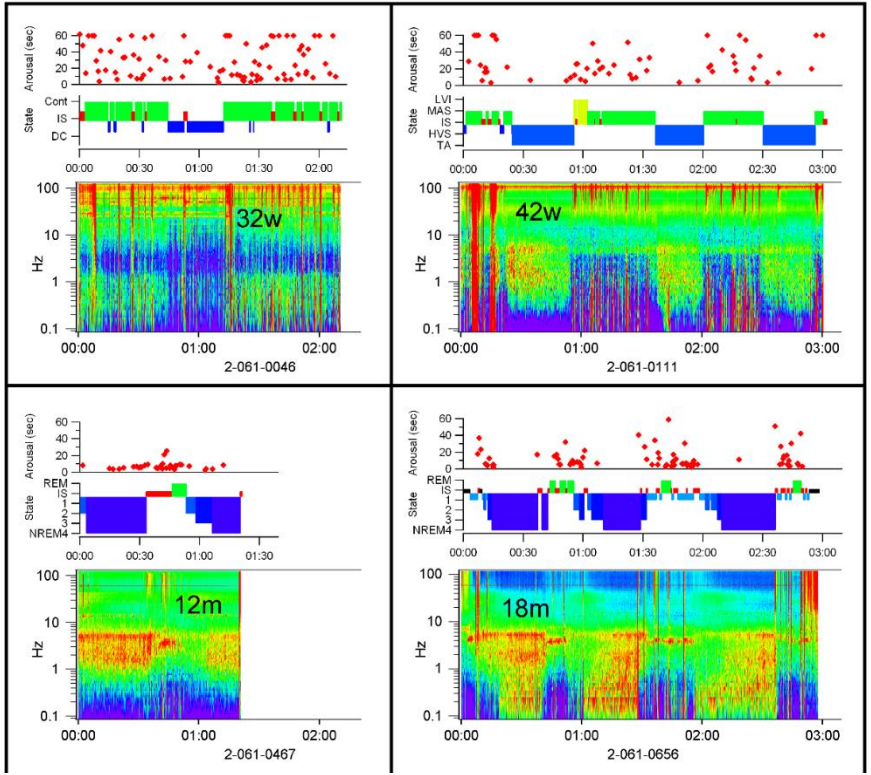
Prenatal
- fetal medication, dexamethasone for fetal lung maturation
- femoral dysplasia
- IUGR, severe

Labor & Delivery
- c-sectionl
- presentation, breech

Perinatal
- APGAR 4&8
- length 33 cm
- weight 710 g
- OFC 25 cm

Placental
- focal accelerated villous maturation for GA
- SGA, combined
- dizygotic, fused, dichorionic, diamnionic

Four of six longitudinal EEG/Sleep Studies from a 26 week GA ♀



Brazy = 3 (for ventilator and infection)

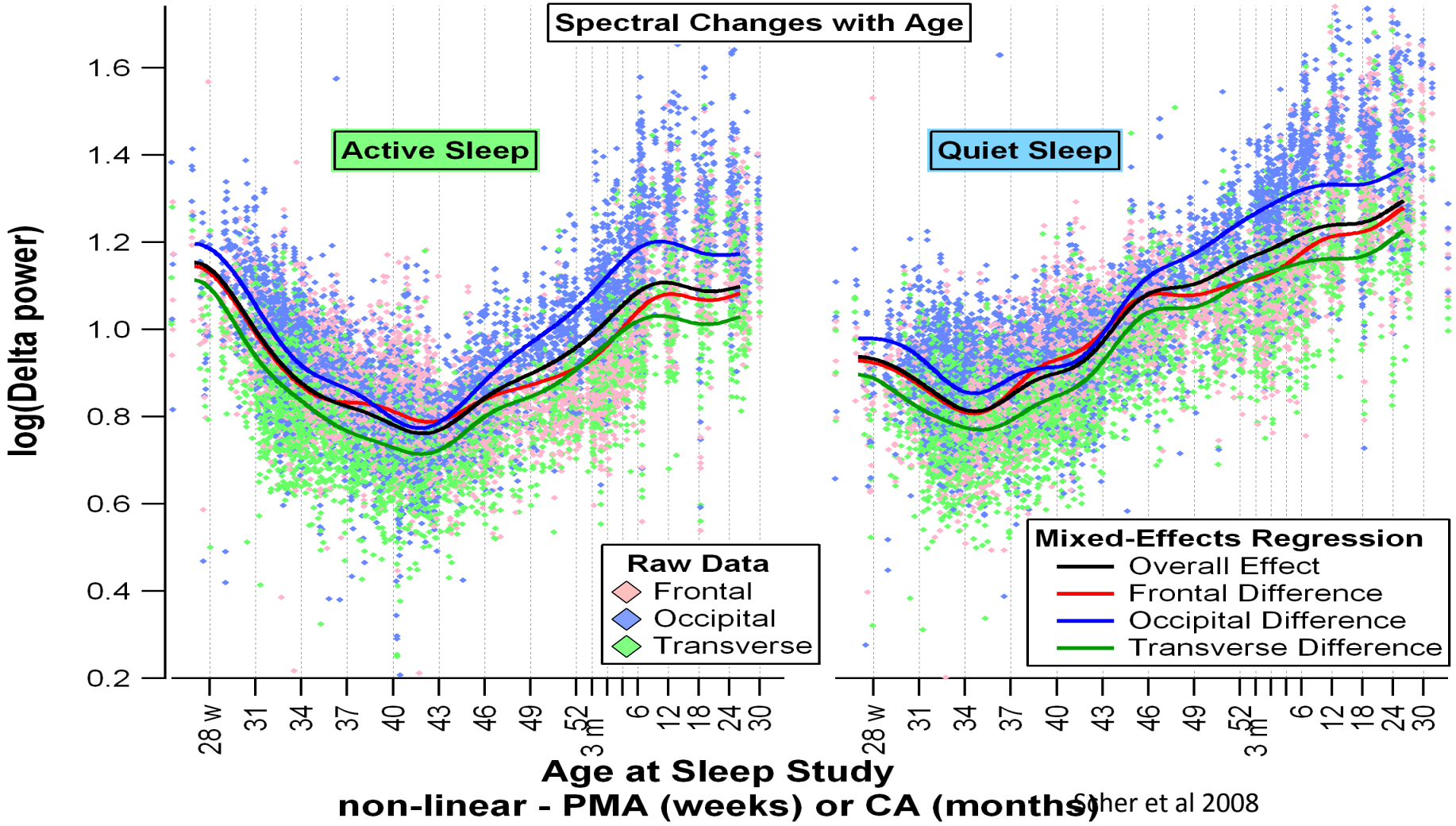
	Bayley		PLS-3		
Age	**Mental**	**Motor**	**Aud**	**Expr**	**Total**
9m 4d	101	104			
19m 0d	75	70			
24m 27d	88	96	97	77	86

Postnatal
- hypoglycemia at birth
- focal femoral dysplasia
- question of low set ears
- long hx of feeding intolerance
- gallstones
- mild dolichocephaly
- small groove in palate
- hyperreflexia
- hypertonia
- anemia of prematurity
- congestive heart failure
- patent ductus arteriosus
- chronic lung disease
- respiratory distress synd.
- Hyperbilirubinemia(6.2)
- apnea of prematurity
- umbilical hernia
- enterococcus septicemia

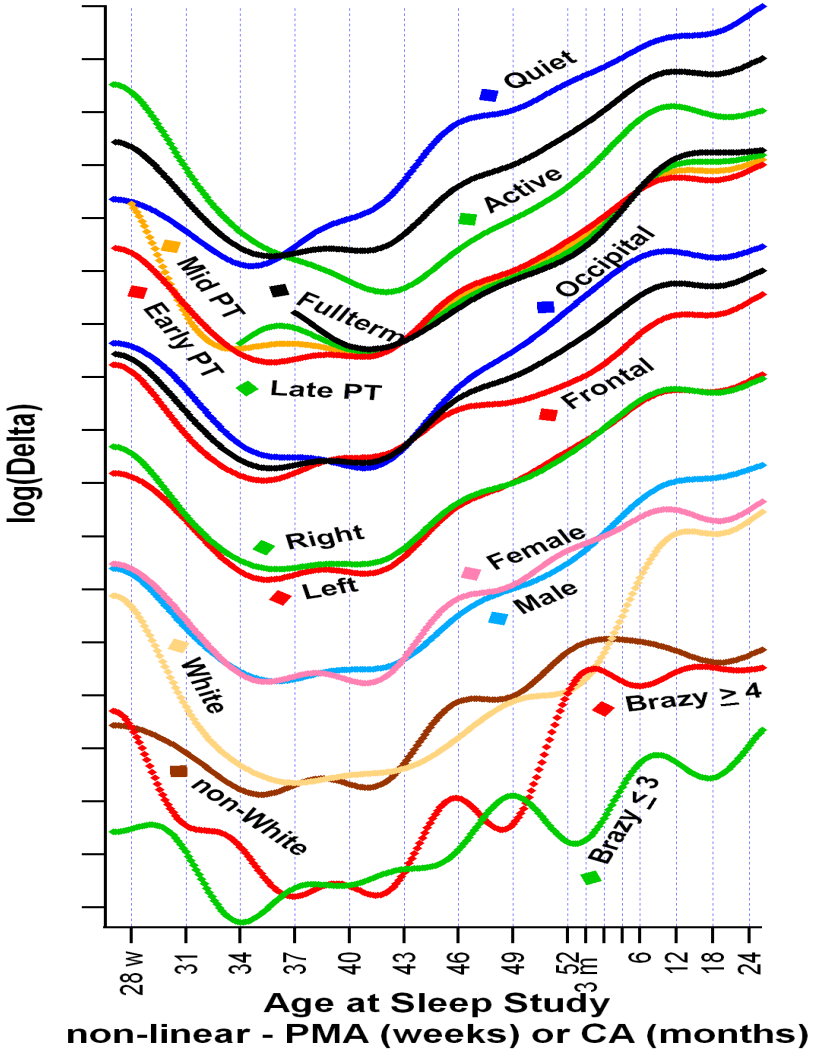
Hospital Discharge
- DOL 104
- length 45 cm
- weight 2830 g
- head cir. 32 cm

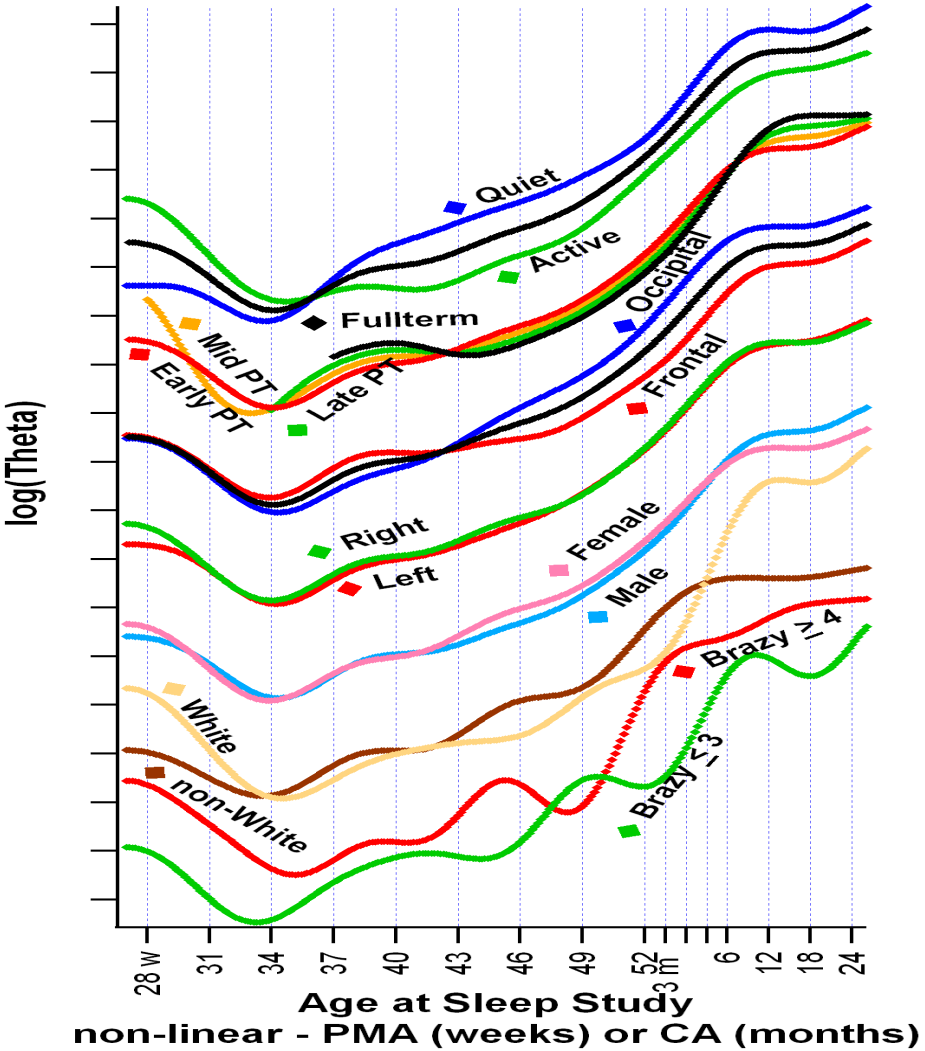
Radiology
- **echocardiogram**
  - small PDA with PFO
  - PFO with peripheral pulmonic stenosis
- **head ultrasound**
  - normal x5

Eye Exam
- normal retina



Scher et al 2008


log(Delta)
Quiet
Active
Mid PT
Early PT
Fullterm
Late PT
Occipital
Frontal
Right
Left
Female
Male
White
non-White
Brazy ≥ 4
Brazy ≤ 3
28 w
31
34
37
40
43
46
49
52
3 m
6
12
18
24
Age at Sleep Study
non-linear - PMA (weeks) or CA (months)


log(Theta)
Quiet
Active
Fullterm
Mid PT
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Occipital
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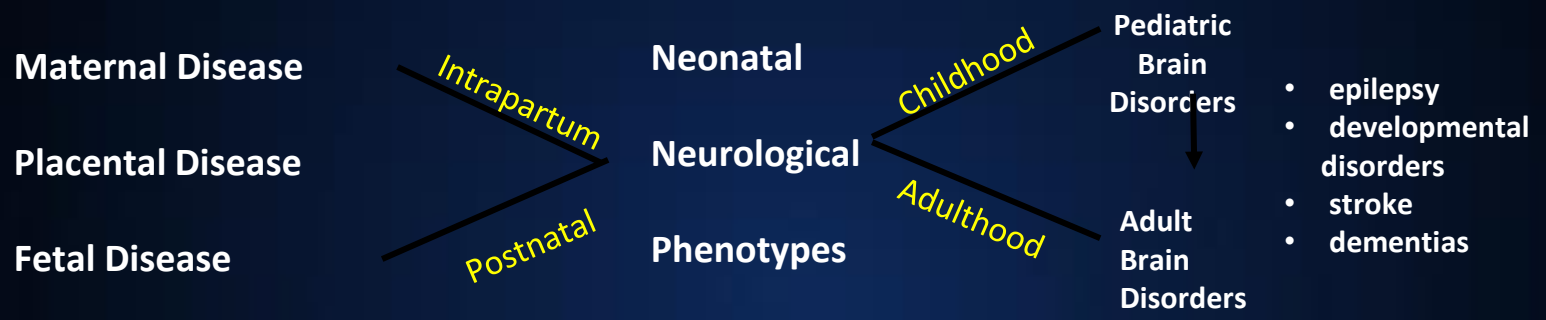
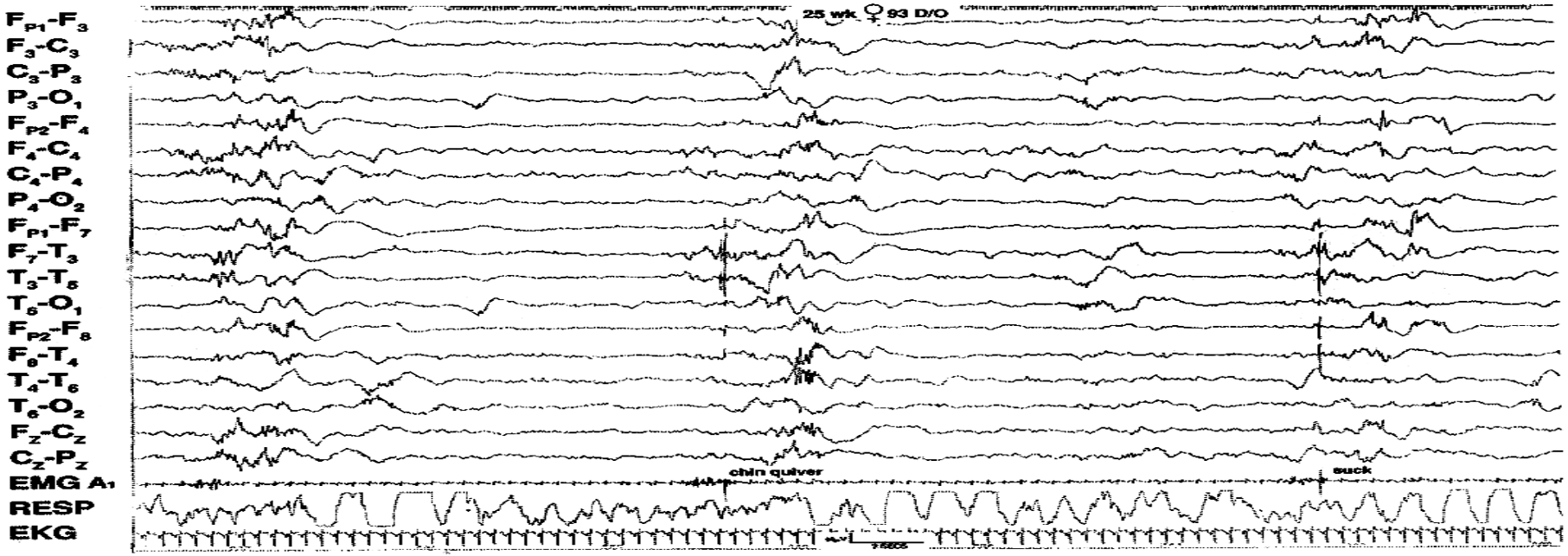
Age at Sleep Study
non-linear - PMA (weeks) or CA (months)

EEG-SLEEP – Endophenotype (G x E)

Surrogate Biomarker for Past-Present-Future Brain Health or Disease



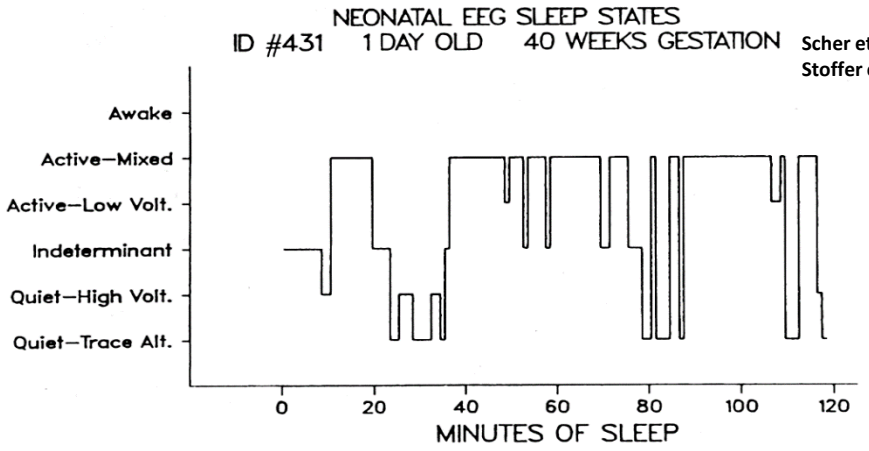
- antepartum-peripartum-intrapartum-neonatal factors express the phenotype
- encephalopathy of prematurity- developmental + destructive processes
- life-long consequences-developmental origins of brain health/disease



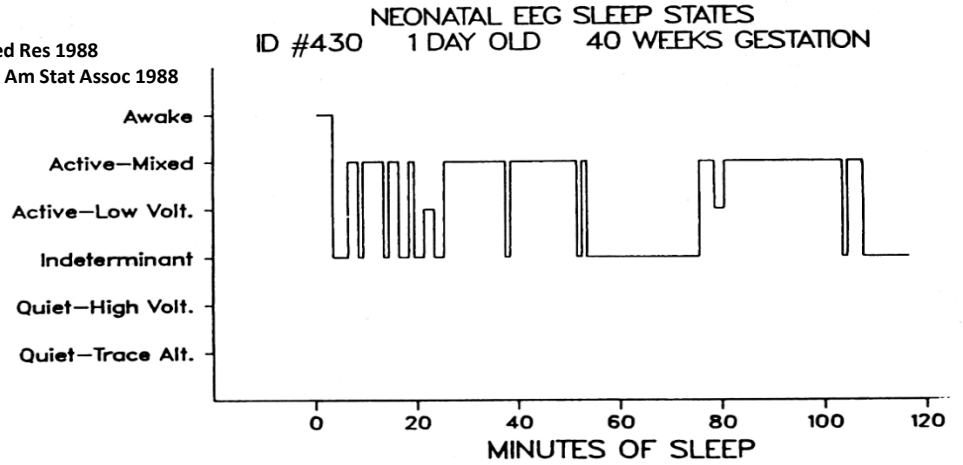
- CLD, IVH, PVL; exam by term corrected age hypotonia
- EEG/sleep dysmaturity
  - ➔ lack of background
    - excessive delta brush patterns
  - ➔ asynchrony
- Neurodevelopment delay (3 years) -Tharp, Scher, Clancy 1989
- Endophenotype of combined prenatal/postnatal factors, expressed as dysmaturity

Effect of Prenatal Substance Exposure on Brain Development

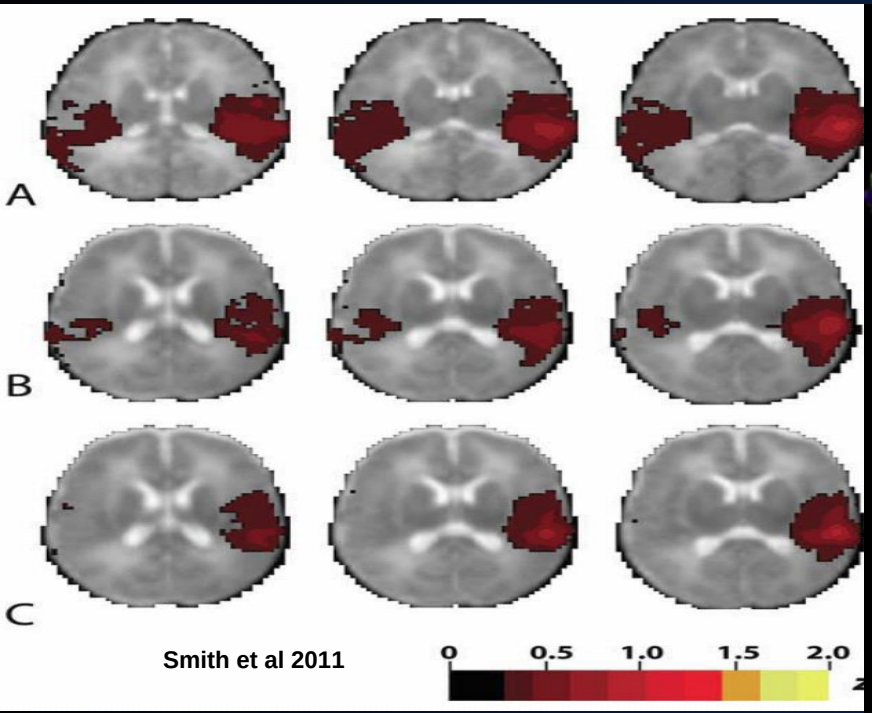
- Maternal Health Practices and Child Development Project NL Day-PI- Behavioral Teratology Program
- Prenatal Substance Exposure as a biomarker for prenatal maternal/placental/fetal health risks
- Consider the complex interactions of biological and social factors
- 860 maternal-child pairs trimester-specific substance exposure-follow-up into adulthood
  - No abstinence syndrome or dysmorphic features of FAS
  - Subset (N=74) received neonatal EEG/SLEEP studies and VERs
- Described physiologic dysmaturity of sleep cyclicity and delayed visual pathway expressed by asymptomatic neonates
- Endophenotype of EEG/sleep representing complex interactions between maternal-child pairs



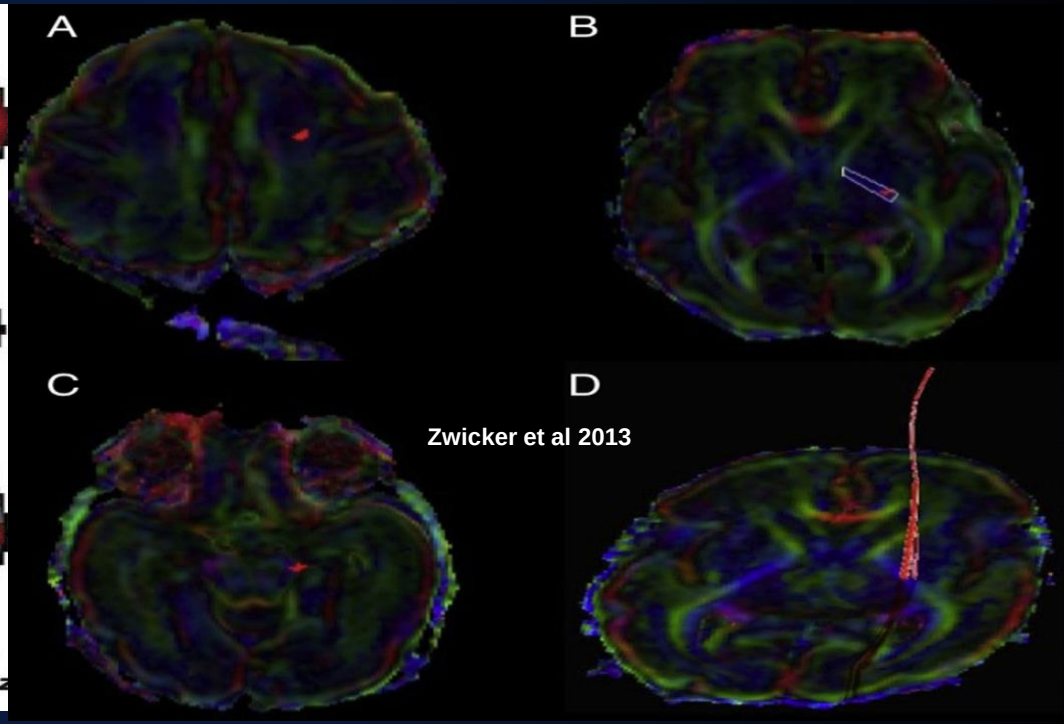
Scher et al Ped Res 1988
Stoffer et al J Am Stat Assoc 1988



Imaging Endophenotypes of Postnatal Illness



Smith et al 2011



Zwicker et al 2013

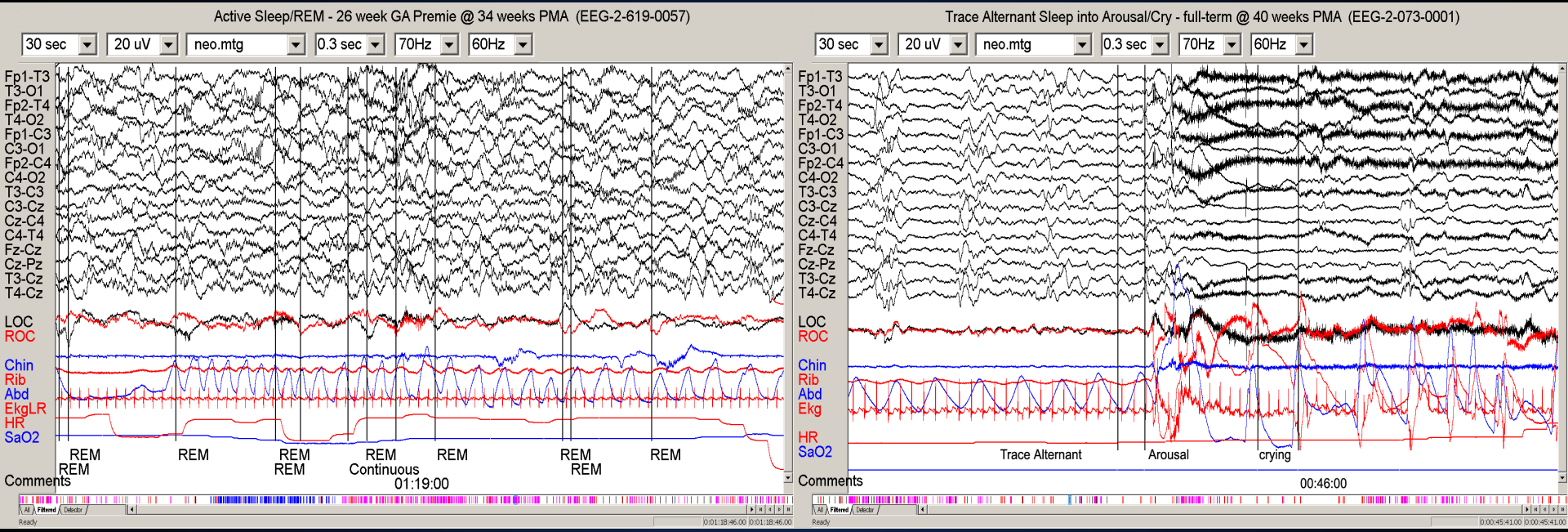
NICU Stress Scores until term ages

- Smaller cortical widths,
- Reduced brain connectivity
- Altered motor and neurobehavior using MRI-metrics, diffusion, fMRI

Snapp II clinical illness scores at 24 hours of life

- Slower rise in fractional anisotropy of corticospinal tracts

EEG/sleep Endophenotype to Assess Neuroprotection by Skin to Skin Contact



Single Skin to Skin Session

improved sleep organization at 32 weeks GA

- decreased arousals
- decreased REMs
- decreased indeterminate sleep segment Ludington-Hoe et al *Pediatrics* 2006

EEG-SLEEP Analyses Over Eight Weeks of SSC on Preterm Infants

- decreased REMs
- decreased arousals
- increased respiratory regularity
- increased spectral beta power

- Increased computational complexity- three regions of the right hemisphere
  - Scher et al Clin Neurophysiol. 2009

- Increased EEG complexity after serial SSC validated using discriminant analysis between groups Kaffashi et al Clin Neurophysiol 2012

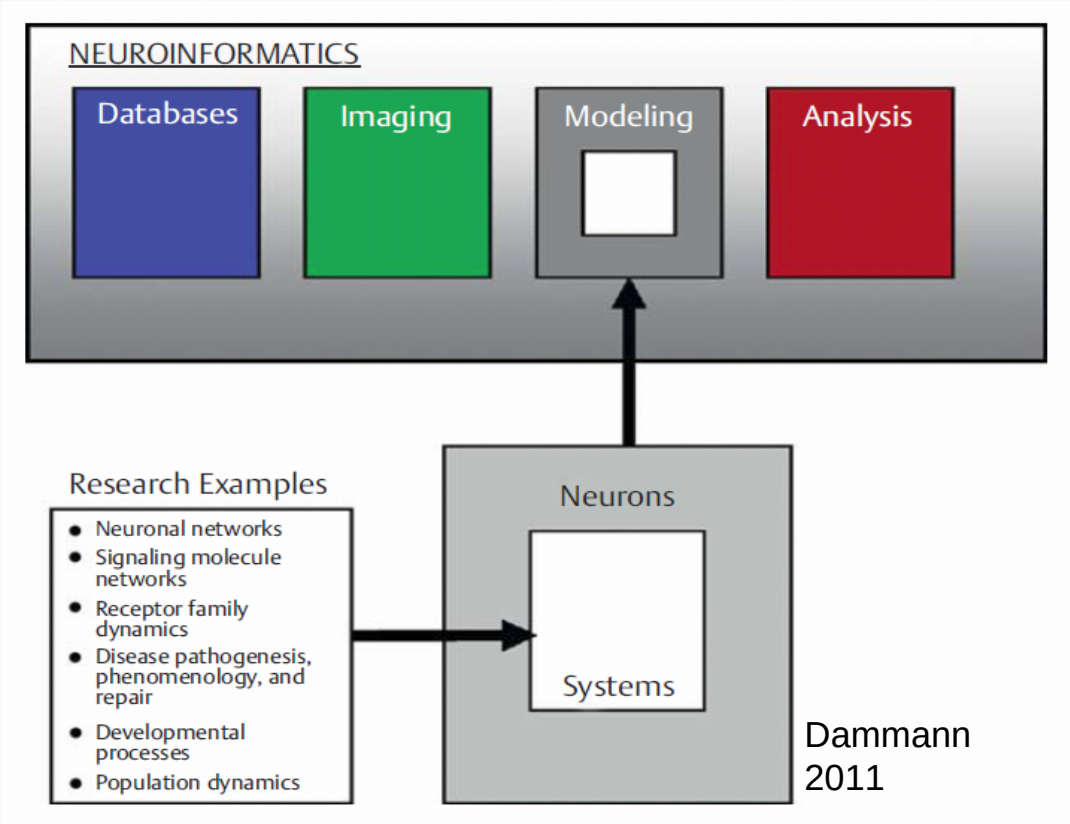
- Implications for NICU sensory enrichment
- Potential application to assess efficacy of other neurotherapeutic interventions

Apply Multiple Biomarkers to Assess Brain Development/Aging-NEUROINFORMATICS

- **Multi-scale computational Monitoring-clinical, genetics, imaging, neurophysiologic databases**

- **Track brain structure/function from fetal life through adulthood**

- **Apply to life-course research from fetal to old age to assess outcome and effects of neurointerventions**



Dammann 2011

Fig.1 Neuroinformatics focuses on the use of computer-based strategies in highly data intensive projects.

Life-Course Connectome of Brain Health and Disease Begins with Fetal/Neonatal Health

- **Age/region-specific brain networks combine visual/digital analyses to assess G x E with maturation**
- **Identify genetic/epigenetic markers with greater connectivity changes during critical/sensitive periods of pre- and postnatal brain development**
- **Longitudinal birth cohort studies (e.g. AGES) combine prenatal G x E maternal/placental/fetal/neonatal effects with postnatal factors to alter old-age ICV/cognitive function**
- **Apply normative brain connectomes to neurotherapeutics trials across the life span to preserve brain health by preventive, rescue or repair protocols**