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
### Principal component analyses of EEG and 5 sonographic measures

#### A. Eigenvalues of the correlation matrix

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<thead>
<tr>
<th></th>
<th>Eigenvalue</th>
<th>Difference</th>
<th>Proportion</th>
<th>Cumulative</th>
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<td>4.34168</td>
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#### B. Eigenvectors

<table>
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<tr>
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<tbody>
<tr>
<td>Head</td>
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<tr>
<td>Biparietal</td>
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<tr>
<td>Femur</td>
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<td>Abdominal</td>
<td>0.423258</td>
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Maturation of Transient Fetal Brain Structures Affected by Prematurity

- 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-oligodendrocyte 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 thalamocortical 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
27 wk GA
38 wk CA

30 wk 5 days

30 wk 9 days
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
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
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 rhythms predominant for the neonate
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 and Johnson 2005
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)
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)

**HR Ratio of Harmonics in Infants at Term**

**RR Ratio of Harmonics in Infants at Term**

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
Analytic Strategies to Depict Brain Organization/Maturation

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

Scher et al 1990

Turnbull et al 2001

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-section
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

Bayley
Age Mental Motor
9m 4d 101 104
19m 0d 75 70
24m 27d 88 96

Eye Exam
normal retina

Brazy = 3 (for ventilator and infection)

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

Longitudinal EEG/Sleep Studies from a 26 week GA

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

Brazy = 3 (for ventilator and infection)

Bayley
Age Mental Motor
9m 4d 101 104
19m 0d 75 70
24m 27d 88 96

PLS-3
Aud Expr Total
97 77 86
Spectral Changes with Age

Active Sleep

Quiet Sleep

log(Delta power)

Age at Sleep Study
non-linear - PMA (weeks) or CA (months)

Scher et al 2008

Raw Data
- Frontal
- Occipital
- Transverse

Mixed-Effects Regression
- Overall Effect
- Frontal Difference
- Occipital Difference
- Transverse Difference
EEG-SLEEP – Endophenotype (G x E)
Surrogate Biomarker for Past-Present-Future Brain Health or Disease

Maternal Disease
Placental Disease
Fetal Disease

Intrapartum
Postnatal

Neonatal
Neurological Phenotypes
Childhood
Adulthood

Pediatric Brain Disorders
• epilepsy
• developmental disorders
• stroke
• dementias

Adult Brain Disorders

• 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-Pl- 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

![Graph of Neonatal EEG Sleep States](image-url)
Imaging Endophenotypes of Postnatal Illness

- 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
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

- 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
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.

AGES-REYKJAVIK STUDY
Muller et al 2014