Applications of Complex Systems Biology to the Study of Neural Systems

Kenneth A. Loparo

EECS Department and Case Complex Systems Biology Center

Case Western Reserve University

Cleveland, OH 44106-7071

kenneth.loparo@case.edu

Overview

- **Neural Systems and Development**
  - Activity Dependent Development and Neural Plasticity
  - Complexity as a measure of maturation and neurodevelopment
  - Summary of Results

Plasticity and Activity Dependent Development

- Neural Plasticity is a dynamic process by which the brain develops
- This process is affected by:
  - Nature (e.g. genetic programming)
  - Nurture (e.g. environmental stimulus)
  - Niche (e.g. development)
- Environmental perturbations (e.g. premature birth) can upset this natural process, potentially leading to long-term developmental deficit.

The Developmental Niche

- New brain research suggests the first five years of life are most critical for brain development.

- Synapses, which connect neurons, are created at great speed during the first three years of life.

- The part of the brain responsible for seeing, hearing, speech production and receptive language is most active during the first few years of life.

  - At birth about 25 percent of the brain's connections are formed.

  - By age 3, 90 percent of the brain is hardwired.

- Translational Research Question:

  - What are the effects of genetic and environmental stresses on brain connectivity and long term neural development ?

Complex Systems Biology: An integrative approach to link genotypes and phenotypes with the environment and behaviors through measurements to improve understanding

Measurements:

- EEG Patterns
- Heart Rate
- Blood Pressure
- Temperature …

Genes ·····▶ *Phenotype* ◀···· Environment

Bioinformatics and Computational Genomics

External Stimuli: Positive and Negative Influences

Understanding:

- Biology
- Health
- Development
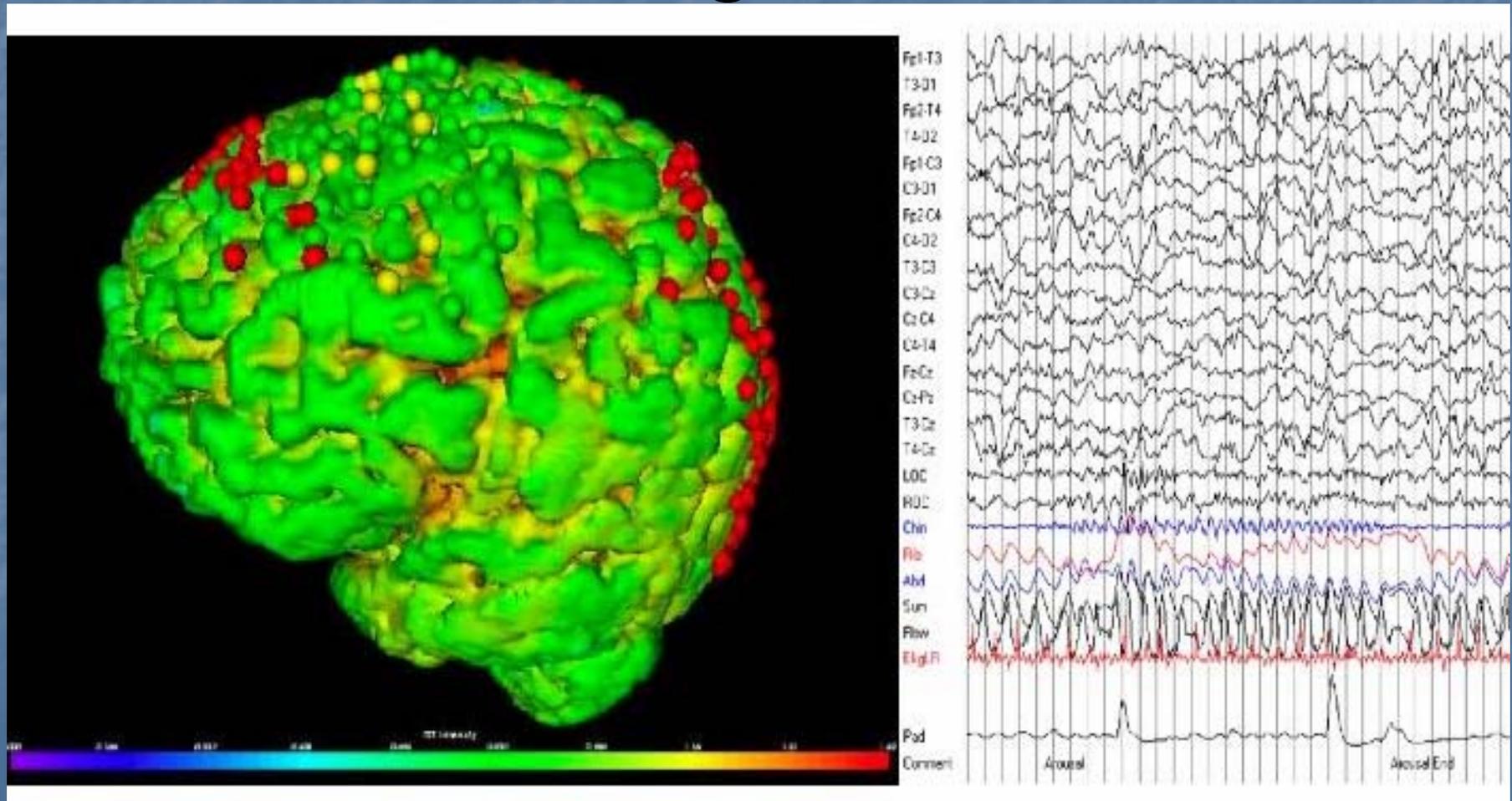- Disease

Complex Network Model
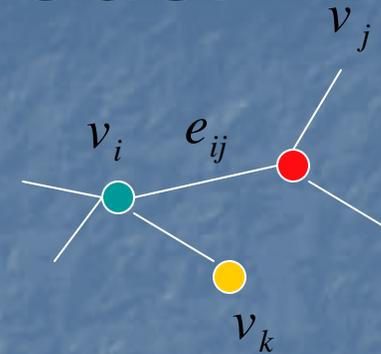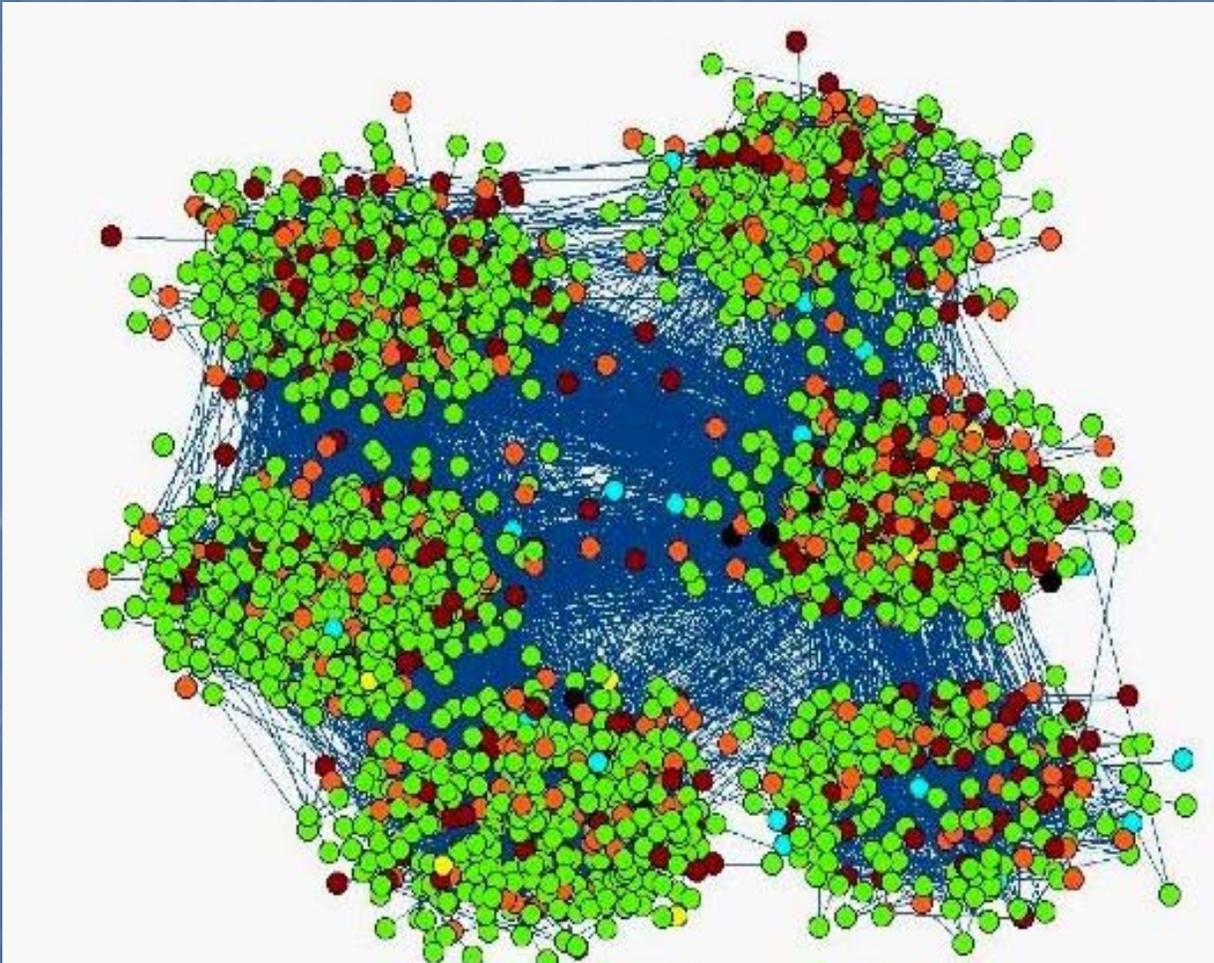
$$N_i = \{v_j\} \text{ such that } e_{ij} \in E$$

Where E = the set of Edges

The degree (k_i)

of node $v_i = |N_i|$

A Measure of Brain Connectivity and Complexity using EEG

The Brain as a Dynamical System

- A dynamical system consists of 2 parts
  - state
  - dynamics
- The state is defined as the information necessary at any given time instant to completely describe the future evolution of the system.
- The dynamics define how the state evolves over time.
- For stable systems, the trajectory of the system approaches a subset of the state space called an *attractor* as time approaches infinity.

Complexity and Dimension

- Geometric properties of the attractor can be used to characterize the system
  - Periodic
  - Quasi-periodic
  - Chaotic
- One method commonly used to quantify dynamical system properties is the *correlation integral* (C_r).
- C_r measures the probability that points on the attractor have pair-wise distances $\leq r$.
- There are two steps to calculating C_r:
  - Step 1: Attractor is reconstructed (embedding);
  - Step 2: C_r is calculated from the reconstructed state vectors.

Attractors and Dimension

- Attractor
  - set of states towards which the system state trajectories are drawn over time – characterizes the long term behavior of the system
- Dimension
  - related to the amount of information required to specify a point on the attractor
- More complex system behavior - more information is required to describe this behavior and the dimension is one way to measure this complexity
- Not all attractors have integer dimension
  - Strange Attractors or Fractals

Correlation Dimension

- At small distances r, the correlation integral behaves as a power of ν, i.e., $C_r \propto r^\nu$.

- The exponent ν is defined as the correlation dimension (D_2).

- The correlation dimension characterizes the active degrees of freedom or complexity of the system.

- The higher the correlation dimension, the more complex the system.

Experimental Measurement of the Attractor

- Measurement of the system attractor

$$y(t)=F(x(t)) : R^k \rightarrow R^m$$

  - k is the dimension of attractor
  - m is the embedding dimension

- Embedding the attractor

  - One-to-one mapping that preserves differential information
  - Also preserves fractal invariants (dimensions, Lyapunov exponents)
  - Guaranteed for m > 2k (Whitney)

Attractor Reconstruction from a Time Series

- **Time Delay Embedding from a one-dimensional time series measurement s(t):**

$$y(t)=H(x(t))=(s(t), s(t-\tau),\ldots, s(t-(m-1)\tau))$$

  - Embedding guaranteed for m > 2k (Takens)

- **Other Methods of Reconstruction**

  - Derivative Coordinates – Decreases SNR
  - Coordinates from Singular Systems Analysis – Increases Ill-conditioning

Correlation Dimension

Correlation Integral:

$$C(r) = \lim_{N \to \infty} \frac{1}{N^2} \sum_{i=1, j=1}^{N} \Theta(r - |x_i - x_j|)$$

- Counts number of pairs of points with inter-point distance less than r

- For small r, $C(r) \approx r^{D_2}$

$\therefore D_2$ = slope of $\dfrac{\log C(r)}{\log r}$ in linear region

Correlation Dimension for Lorenz Attractor, $d_2 = 2.04$

m=2
m=3
m=4
m=5
m=6

m=2, d=1.78
m=3, d=1.95
m=4, d=2.01
m=5, d=2.03
m=6, d=2.07
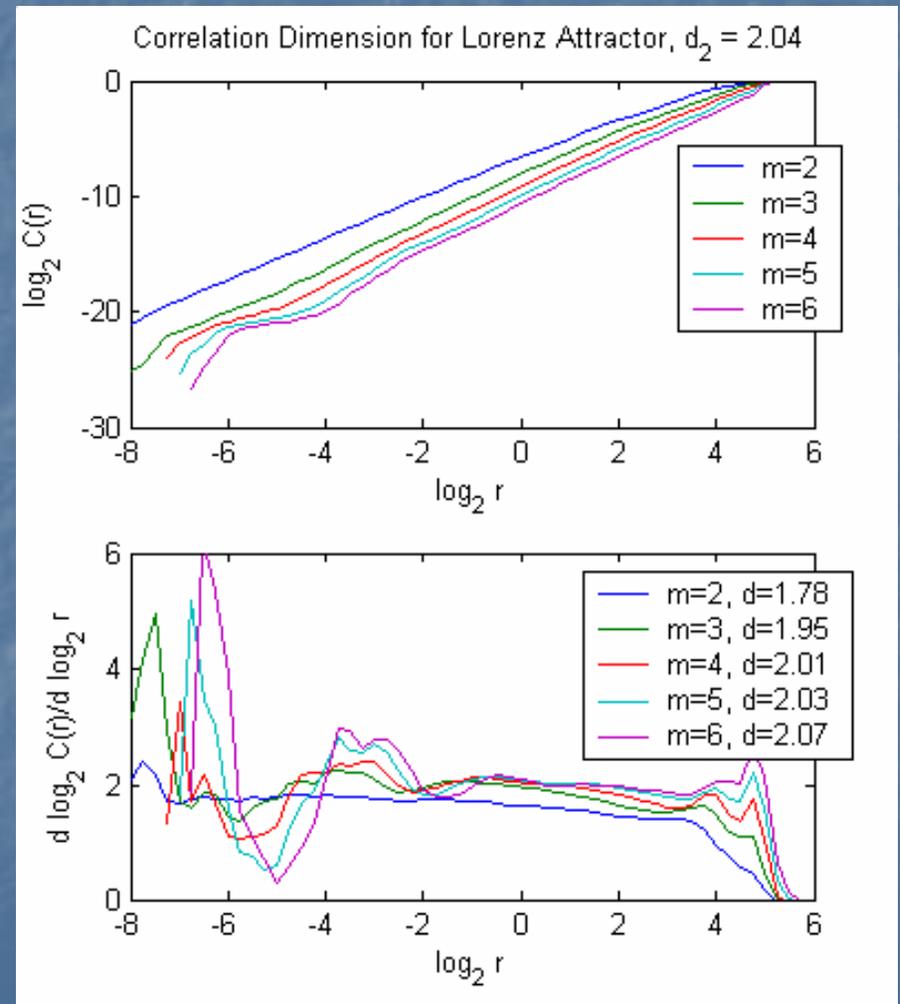
Selection of the Embedding Dimension

- **Goal:** Find minimum embedding dimension required to unfold dynamics of the attractor

- **False Nearest Neighbors**
  - Measures percentage of neighboring points that are close together due to projection of attractor onto subspaces with too small an embedding dimension
  - Okay for selection of minimum embedding dimension
 - Reveals noise level of time series

False Nearest Neighbors for Lorenz Attractor, Impact of Added Noise

Legend:
- no noise
- SNR=40
- SNR=25
- SNR=18
- SNR=8
- SNR=2
- only noise

Y-axis: Percent False Nearest Neighbors
X-axis: Embedding Dimension
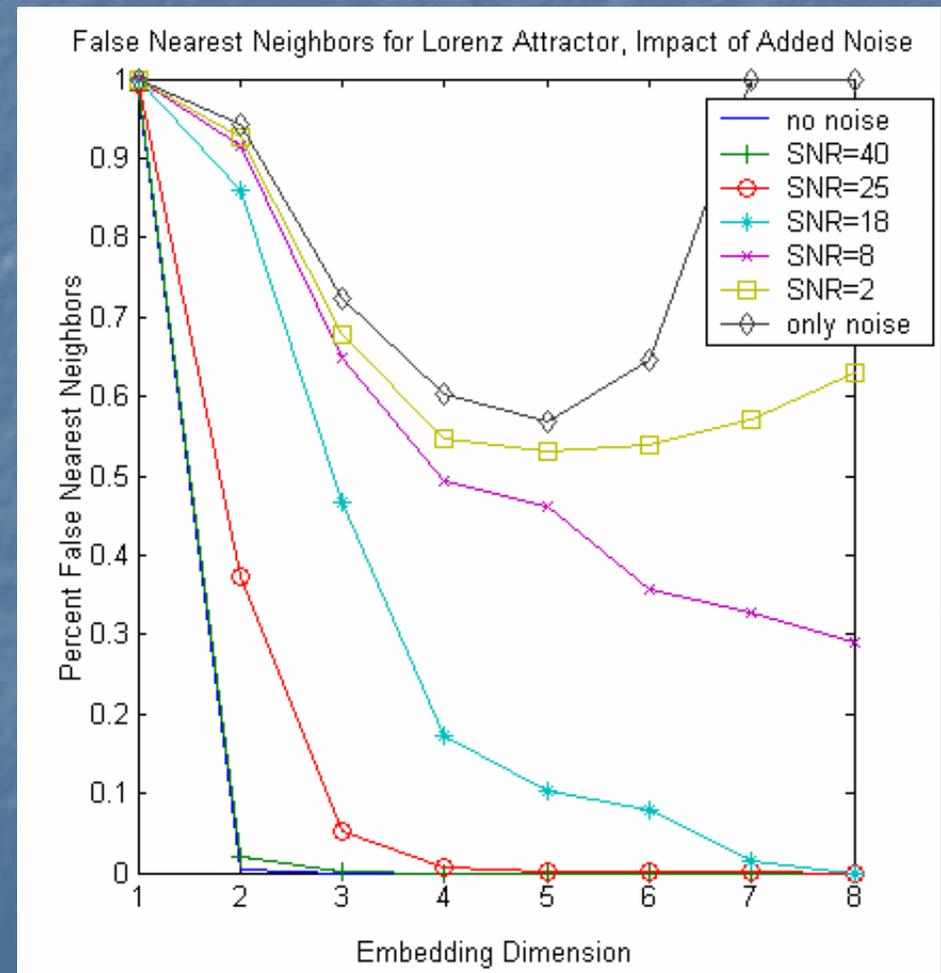
Experimental Study

- EEG data sets: Healthy Neonates born at 31-32 thru full term.

- Data acquisition:
  - Bipolar digital EEG recordings at 12 bits and 64 Hz

- 6 data sets of 3 groups analyzed: full term (FT) (at age 40-41 weeks), preterm (PT) (at age 40-41 weeks) and preterm (PT) (at age 31-32 weeks)

Experimental Analysis

- Time series (EEG) data is segmented into 2-minute epochs
- The epochs for full-term neonates (CA=40-41 weeks) and preterm babies (CA=40-41 weeks) are separated according to their sleep stages, i.e., active sleep (AS) and quiet sleep (QS).
- The epochs for preterm neonates (CA=31-32 weeks) are not grouped by sleep state.
- C_r is computed from the EEG time series using embedding dimensions m=10,12 and 14 while the time delay is varied from 1 to 10 samples.
- The local slopes for the most linear region of the log C_r versus log r provide estimates of D_2.

Results for Channel Fp1-C3
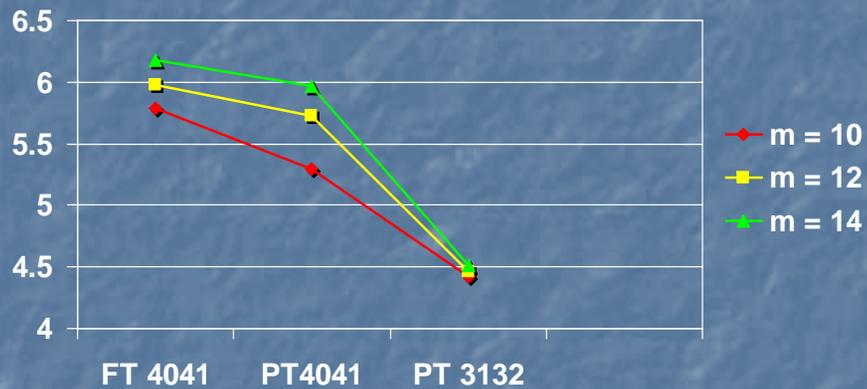
D2 for AS
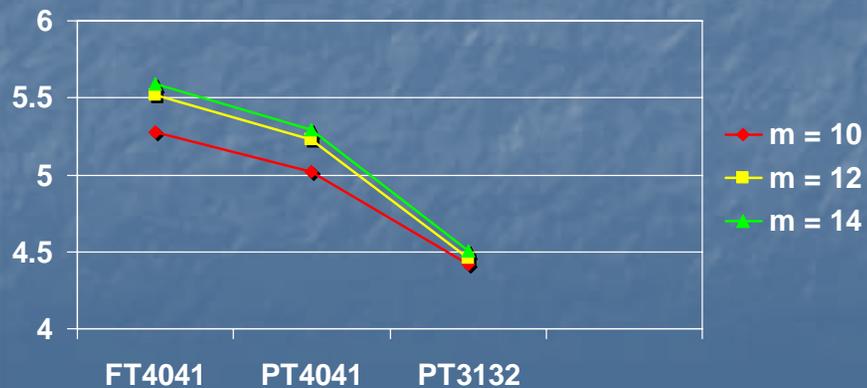
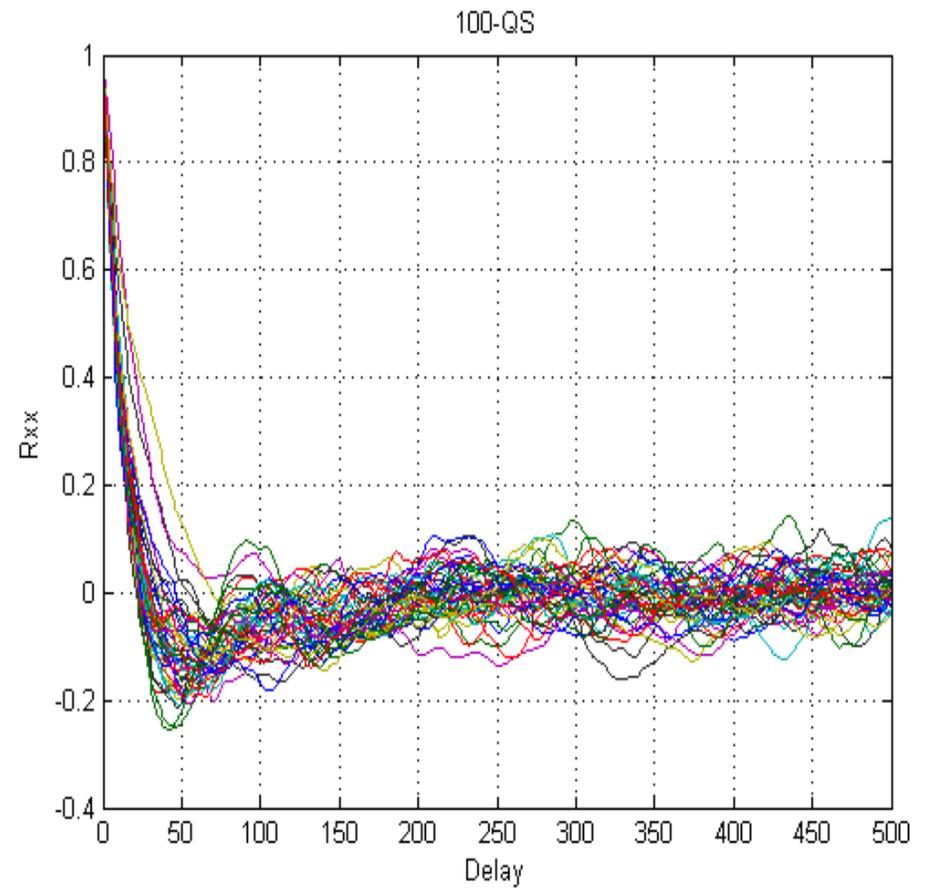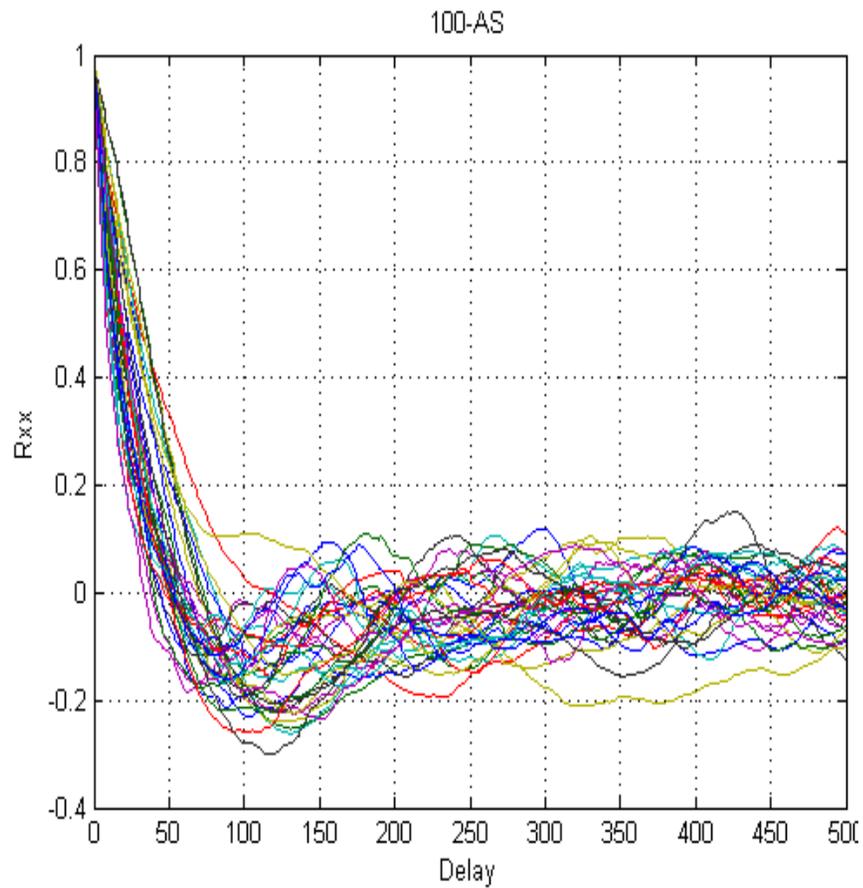| *m*	FT 4041 (AS)	FT 4041 (QS)	PT 4041 (AS)	PT 4041 (QS)	PT 3132
10	5.79 +/- 0.54	5.28 +/- 0.59	5.30 +/- 0.57	5.02 +/- 0.59	4.42 +/- 0.71
12	5.98 +/- 0.61	5.52 +/- 0.61	5.73 +/- 0.63	5.23 +/- 0.64	4.46 +/- 0.73
14	6.18 +/- 0.61	5.59 +/- 0.62	5.9662 +/- 0.62	5.29 +/- 0.62	4.51 +/- 0.71

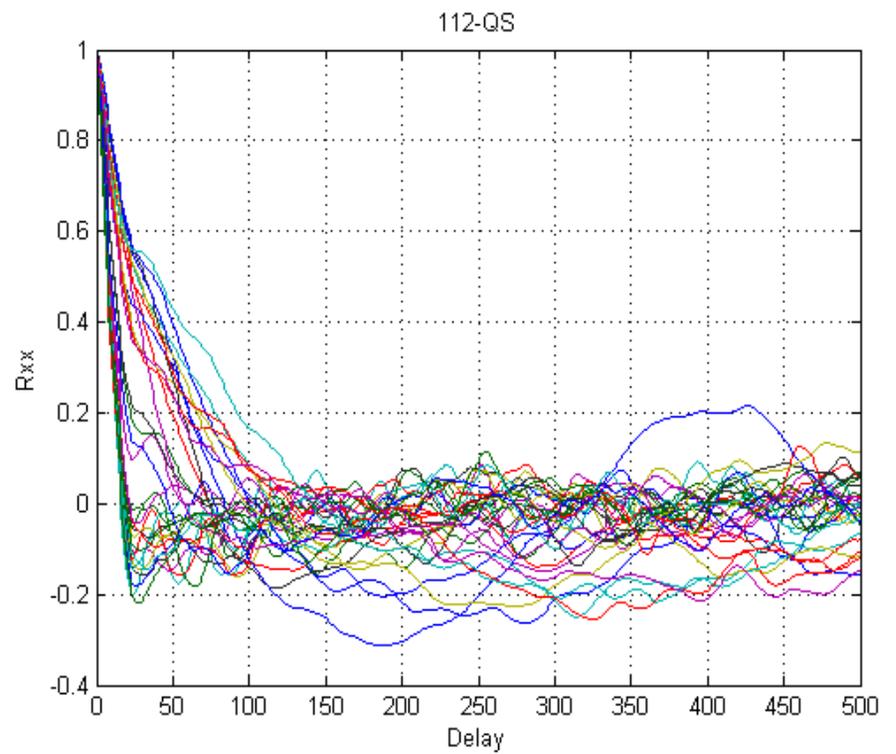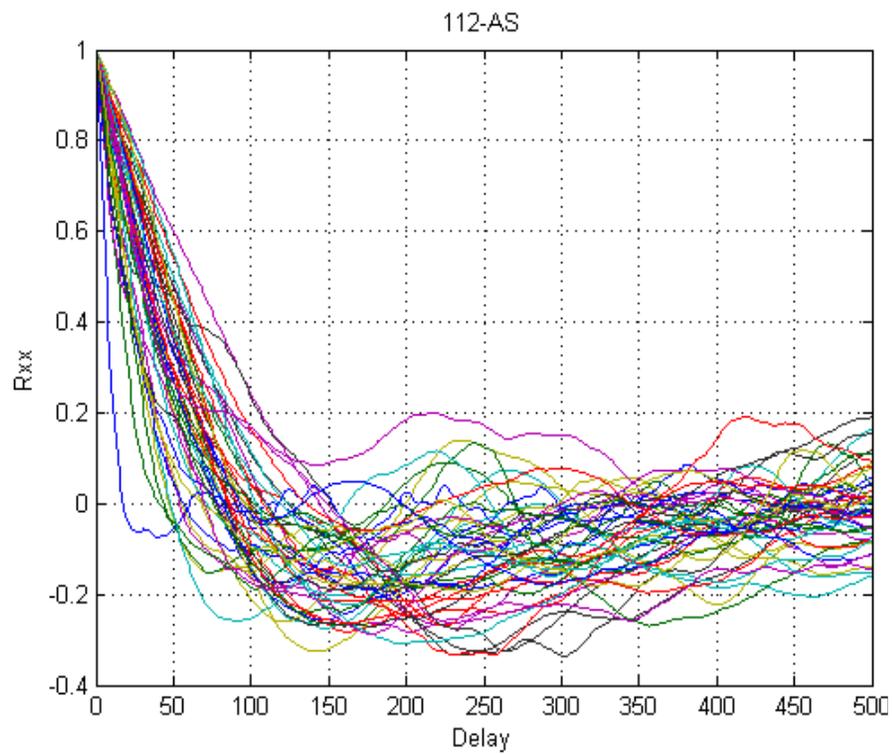**D2 for QS**

Results for Fp1-C3 (AS)
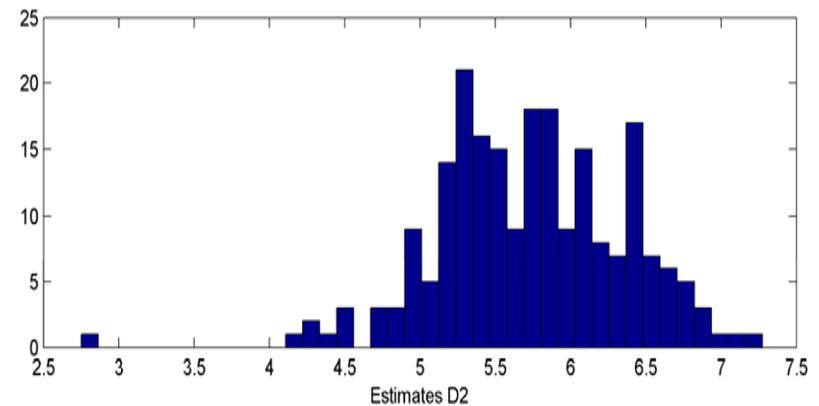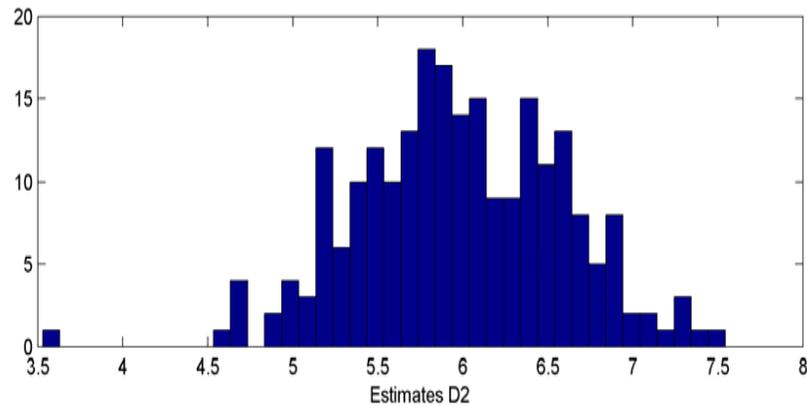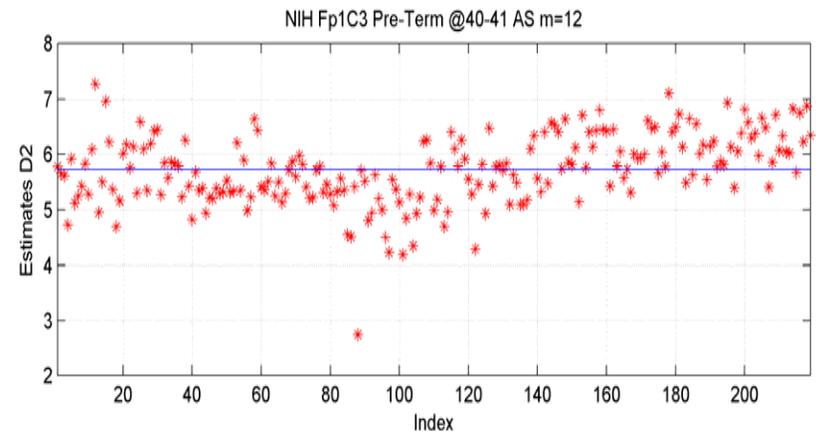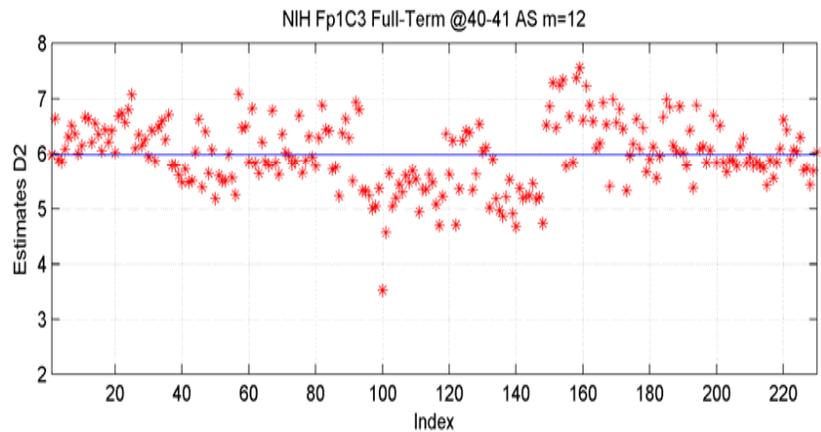
Results for Fp1-C3 (QS)
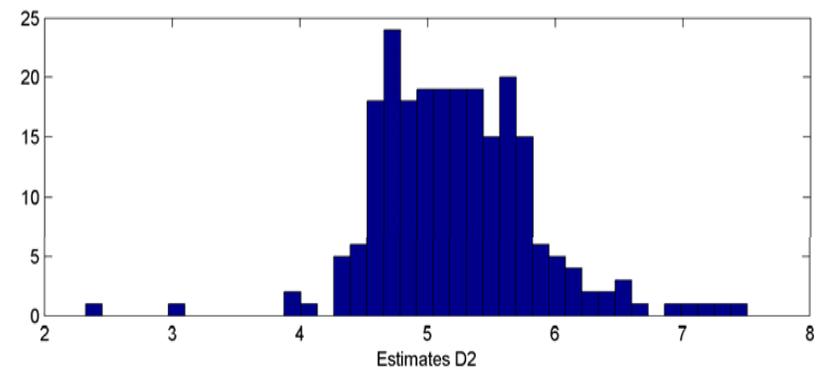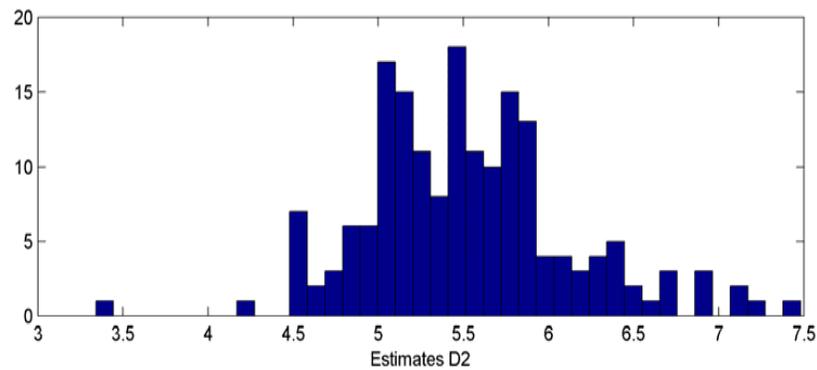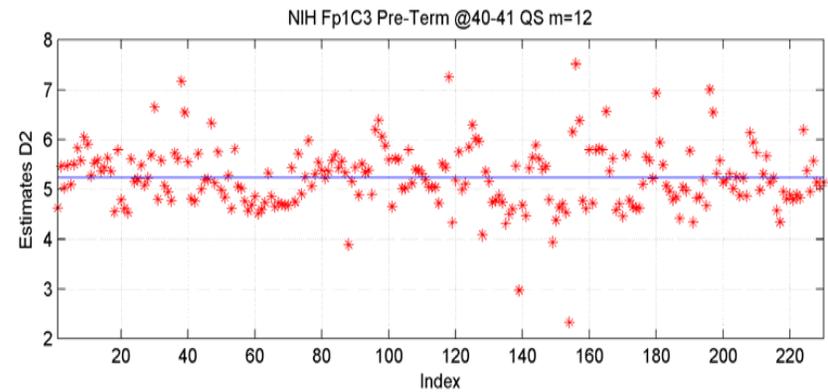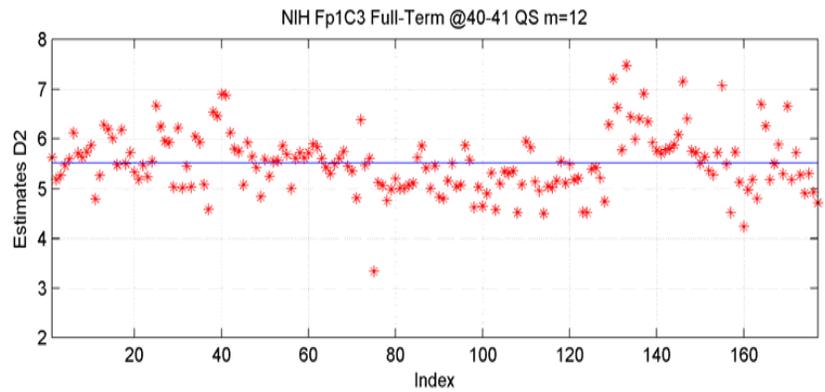
FT4041 R_{xx} (AS & QS)

PT4041 R_{xx} (AS & QS)

Statistical Analysis

T-test for the Null Hypothesis (H_0) that the mean D_2 for FT4041, PT4041, PT3132 and Surrogate data are from the same distribution: 1=reject and 0=can not reject

	FT4041AS	FT4041QS	PT4041AS	PT4041QS	PT3132
FT4041AS	0	1, p<5 e-006	1, p<2 e-04	1, p<1 e-10	1, p<2 e-070
FT4041QS	1, p<5 e-006	0	1, p<1 e-10	1, p<4 e-005	1, p<7 e-066
PT4041AS	1, p<2 e-04	1, p<1 e-10	0	1, p<1 e-007	1, p<1 e-064
PT4041QS	1, p<1 e-10	1, p<4 e-005	1, p<1 e-007	0	1, p<6 e-067
PT3132	1, p<2 e-070	1, p<7 e-066	1, p<1 e-064	1, p<6 e-067	0
Surrogate	0	1, p<4 e-04	0	1, p<1 e-008	1, p<5 e-086

Conclusions: (1) There is a statistically significant difference between FT and PT at same CA (40-41 weeks) (2) PT is less complex than FT, (3) EEG in AS in FT and PT at 40-41 weeks is statistically similar to the surrogate, (4) Complexity of the EEG for FT and PT at 40-41weeks in QS and PT at 31-32 weeks is dominated by nonlinearity.

D$_2$ Complexity and Neural Development
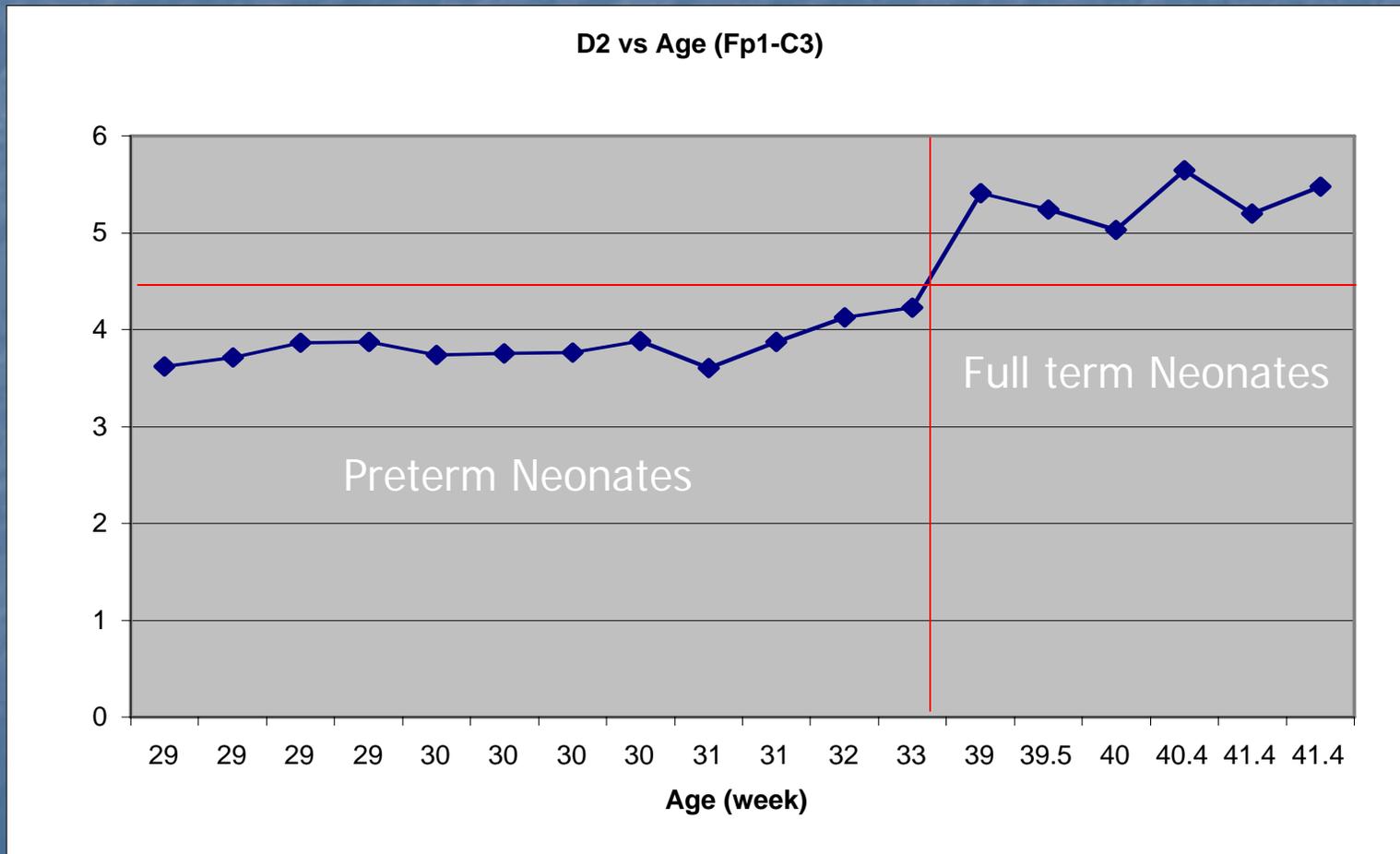
D$_2$ Complexity and Neural Development
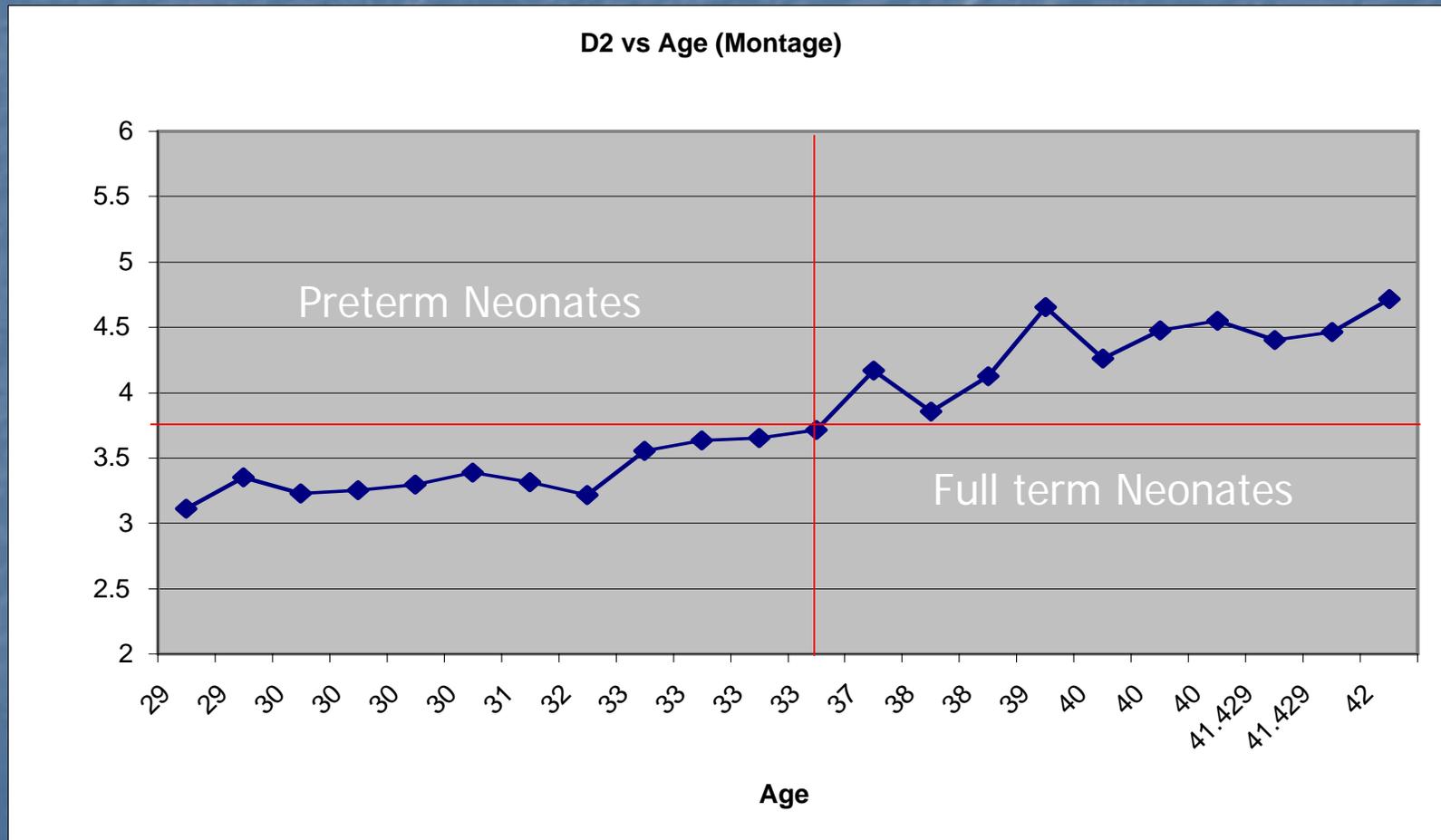
Conclusions

- Plasticity is an activity dependent dynamic process in developing organisms

- Neurodevelopment in neonates can be assessed using a computational phenotype that quantifies "complexity" in the EEG during sleep

- Complexity increases along the developmental trajectory during the neonatal period

Acknowledgements

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Thank You