

Neural Signatures of Autism in High Risk Infants

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Rationale for High-Risk Infants

- Early intervention predicated on early identification
- Behavioral approaches to early identification lack sensitivity and specificity below 12-18 months
- Neural (pre-) markers of autism have advantages of
 - by-passing behavior, which is immature early in life
 - Allowing one to use the same dependent measure from infancy through childhood
 - Examine neural basis of disorder more directly



Overview

- Are particularly interested in using neuroscience and genetic assays, and the intersection of the two
- Proximal Goals:
 - Develop endophenotype for distinguishing low vs. high risk infants¹
 - Create “neurogenomic” profiles of individual children (e.g., 1:5 high risk will develop an ASD but 4:5 will not)
- Distal Goals:
 - Predict which infants will develop autism
 - Examine intersection of genetic and neural markers

¹ high risk is defined as having at least one older sibling with an ASD



Targeted Population

- High risk: infants with at least one older sibling with an ASD
- Low risk: infants with no family history of ASD
- High risk language: infants with at least one sibling with a language impairment (e.g., SLI)

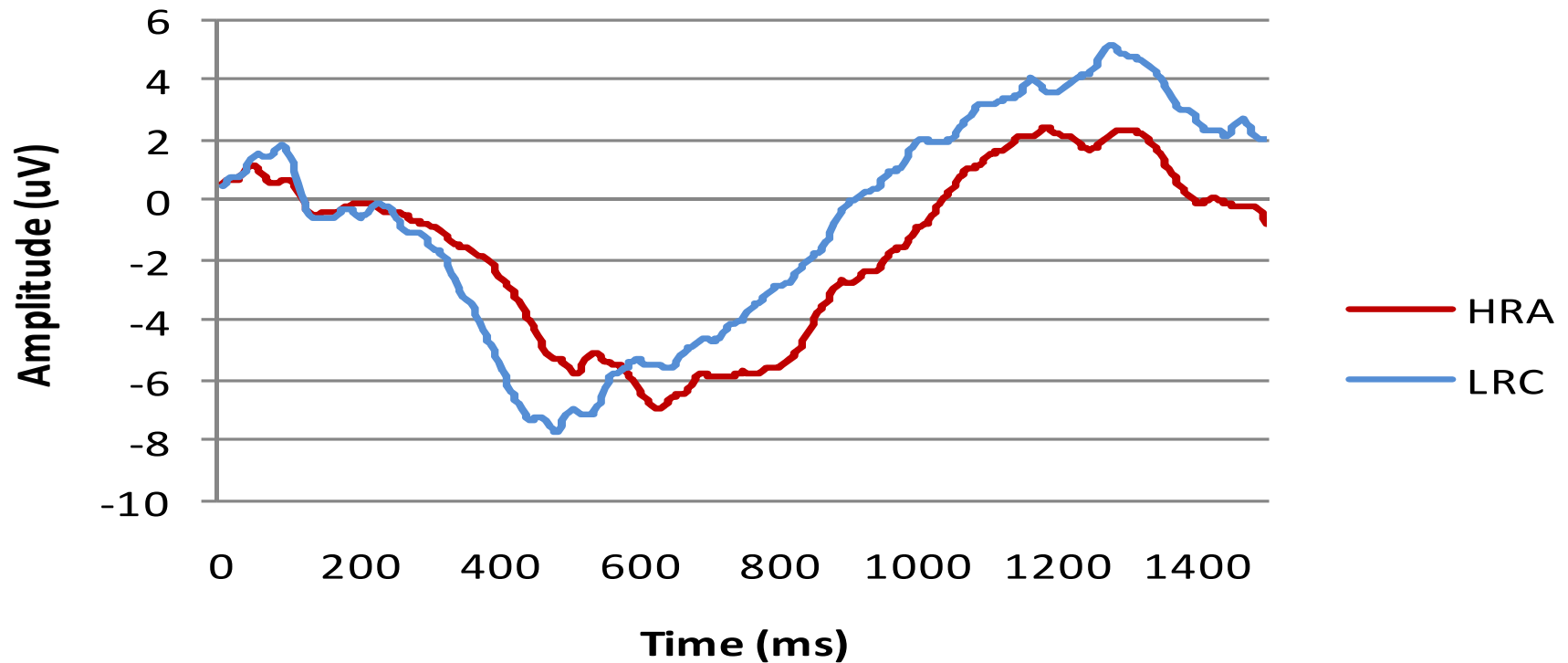
Visual Event-Related Potentials (ERP)

- Design: present alternating pictures of familiar face (mother) and unfamiliar face (stranger)



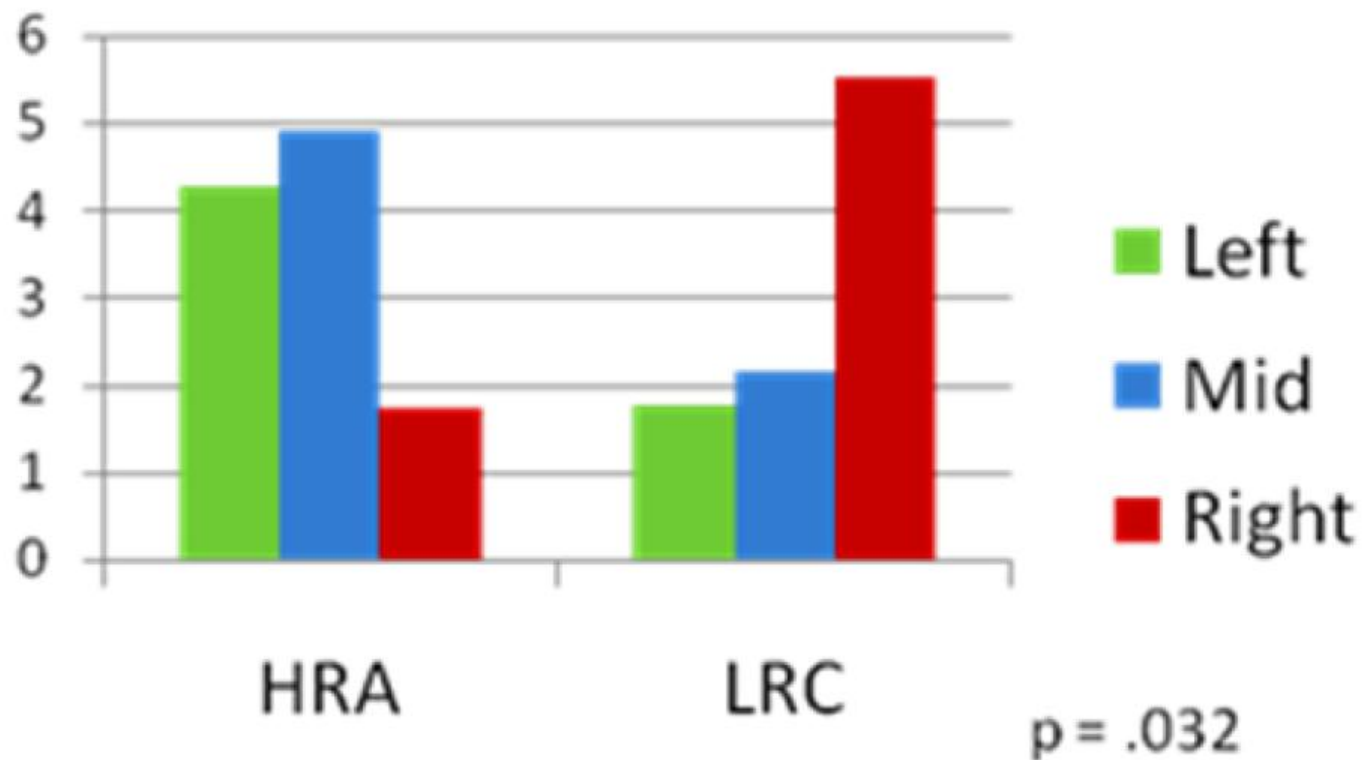
Visual ERP group differences: Nc latency

**6mo NC Latency to Peak
Main Effect of Group**

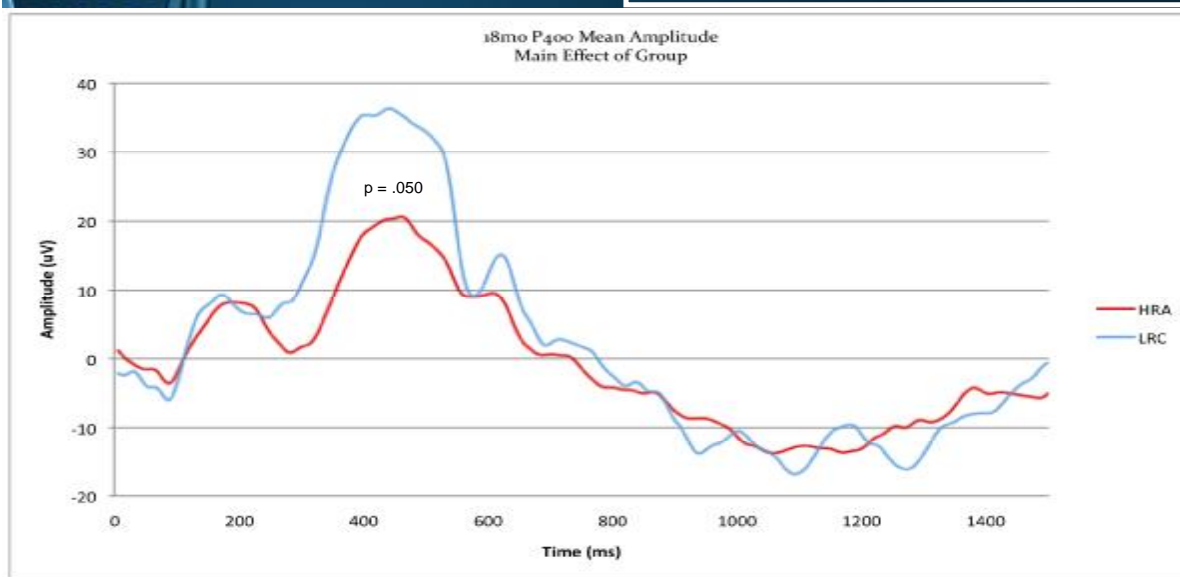
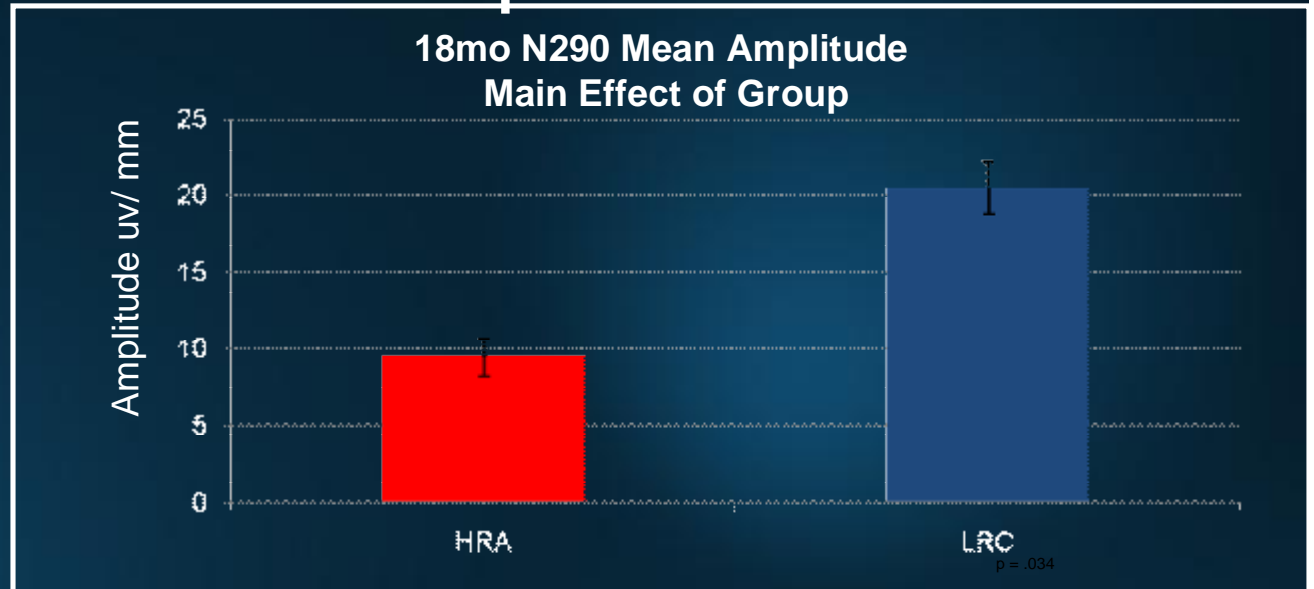


Visual ERP group differences: N290/P400 amplitude

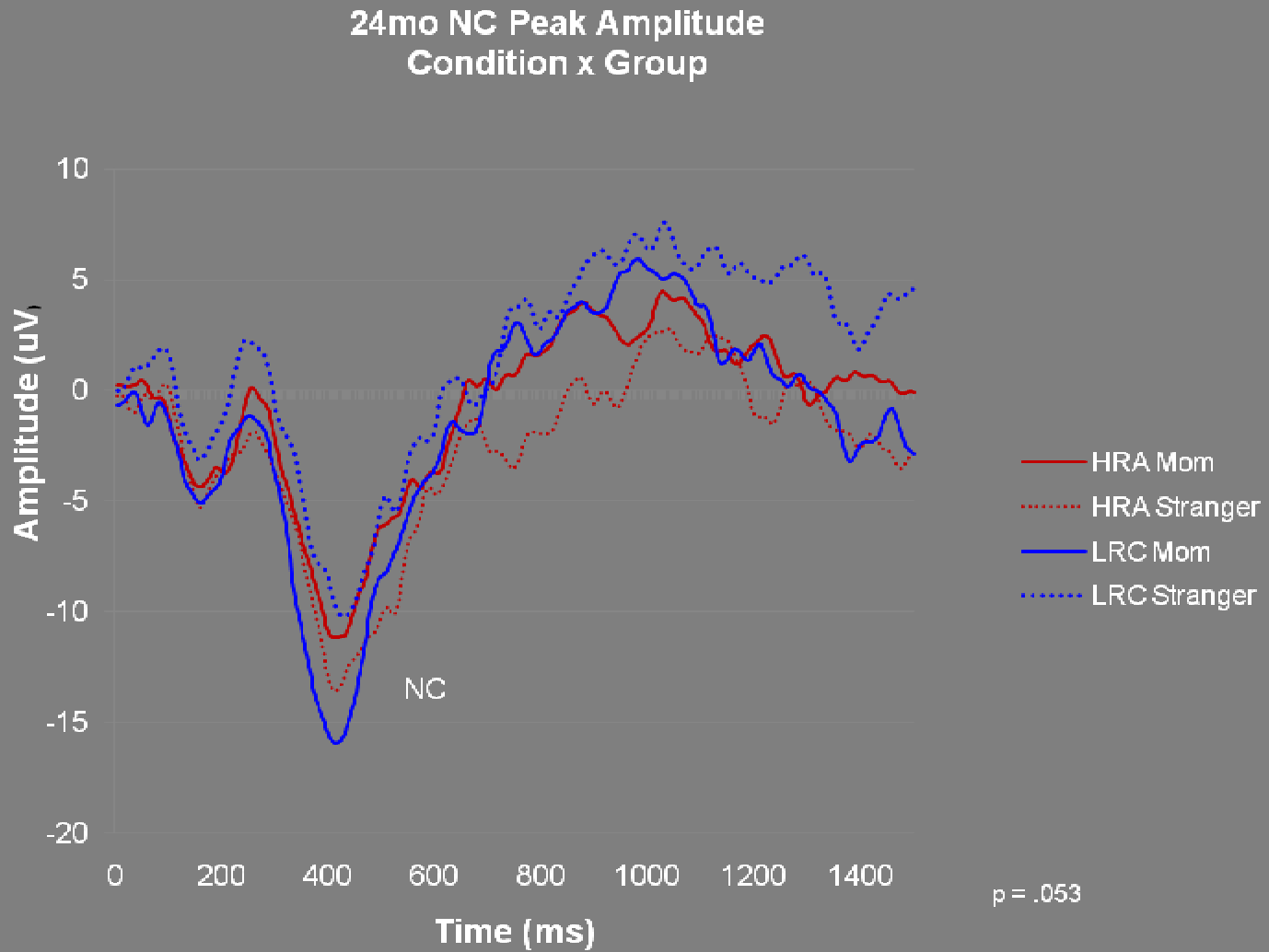
6-month olds: hemispheric differences



Visual ERP group differences: N290/P400 amplitude



ERP responses to mother vs. stranger



For LRC, Mom > Stranger; for HRA, Mom = Stranger



Summary: Visual ERP

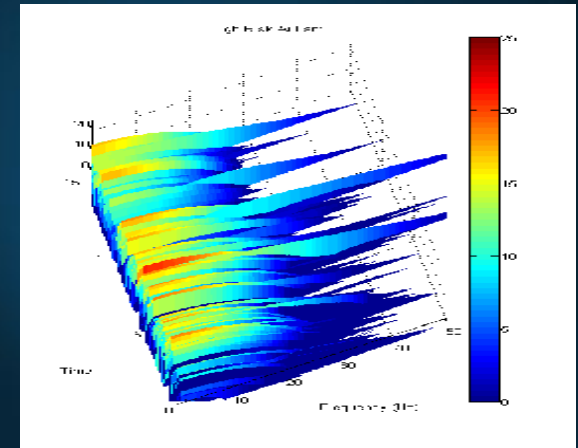
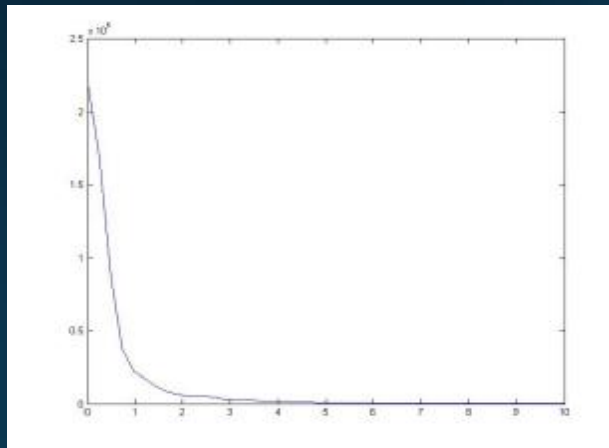
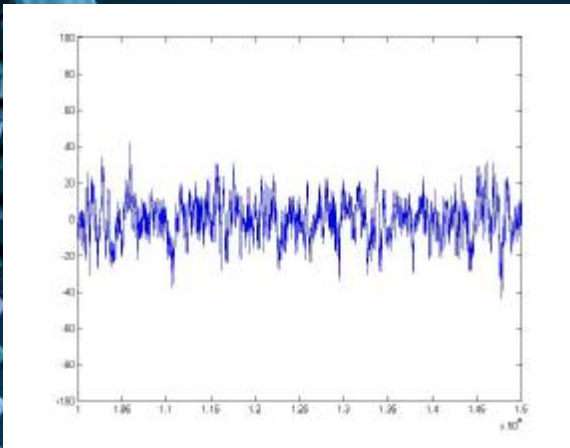
- Low Risk Controls (LRC) differ from High Risk for Autism (HRA) in three ways
 - amplitude NC (attention), N290/P400 (face sensitive):
 - LRC > HRA:
 - latency of NC
 - LRC < HRA
 - Hemisphere differences
 - LRC shows R>L, whereas HRA shows L>R

Electroencephalography (EEG)

- Design: collect baseline EEG



EEG: Time-Frequency Analysis



- Use Fast Fourier Transform (fft) to break down the signal into constituent frequencies
 - This gives the ‘power spectrum’
 - Power is a measure of the energy density in a given frequency range
 - Activity in frequency bands is functionally linked to different behaviors
 - Focus on gamma activity

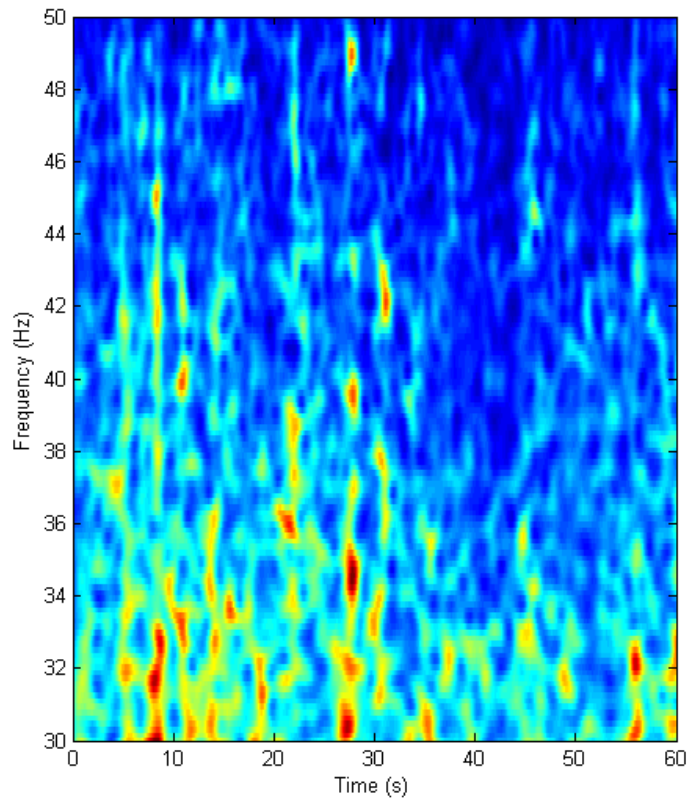


Development of Gamma Band Power

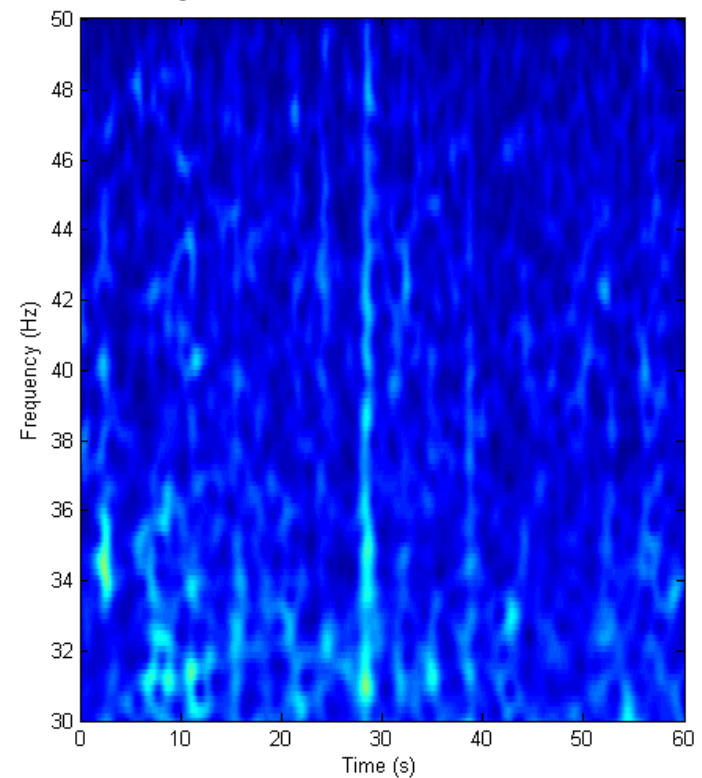
- Gamma represents a binding frequency
 - Connects and integrates information in distributed networks throughout the brain
 - Associated with many cognitive skills: language, executive functions, object permanence
- Autism is considered a ‘disconnection’ syndrome
 - Gamma activity is a useful tool in assessing the levels and patterns of disconnection in individuals with autism
- Current study: developmental trajectories of gamma power
 - Do children at risk for autism have lower levels of gamma power at 6 months and/or are their rates of change in gamma power lower over time?

Comparing gamma activity in 6 month old infants

Low risk control

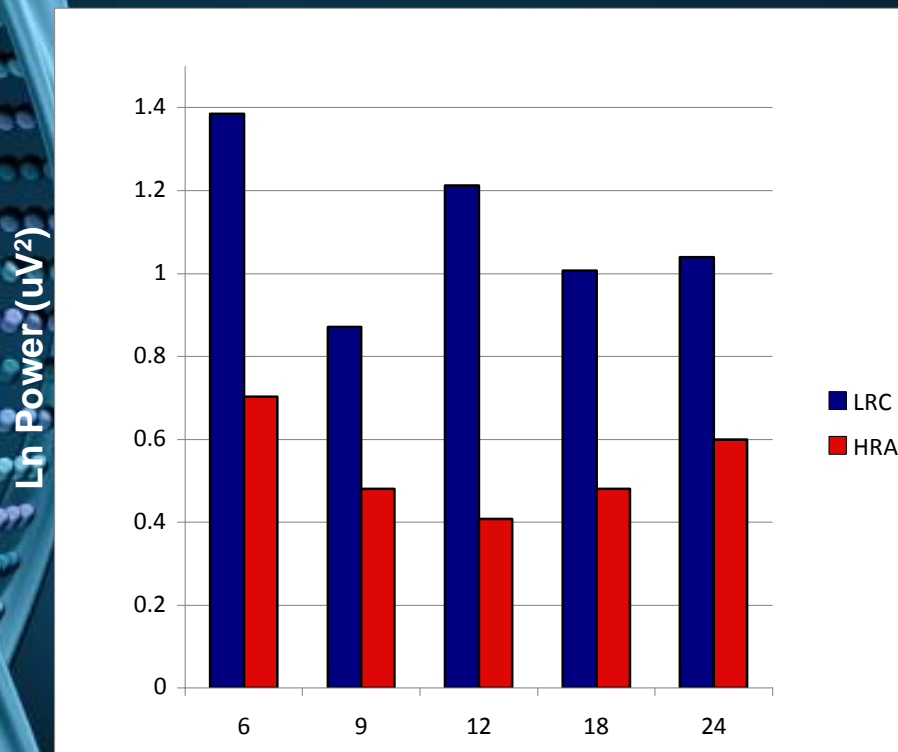


High risk autism

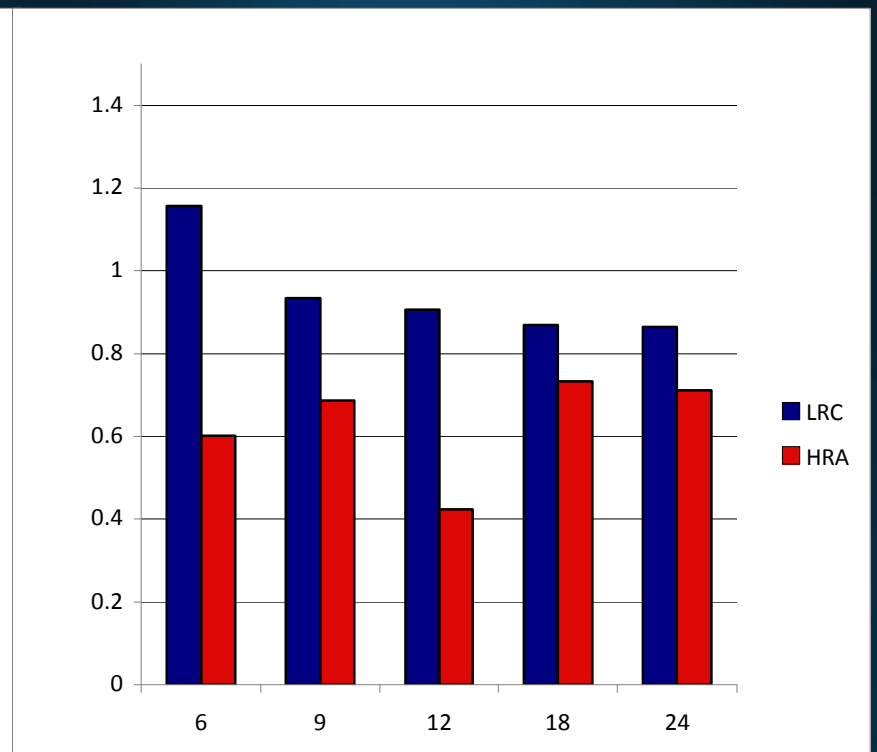


Developmental Trajectories of Gamma Power

Gamma Power Left Hemisphere Gamma Power Right Hemisphere



Age in months



Age in months



Summary: EEG

- Gamma is greatly reduced in HRA vs. LRC infants
- Developmental progression is different for HRA vs. LRC infants



Multiscale Entropy

- Several ways to compute complexity from EEG signals
- Multiscale entropy (MSE) is one useful measure
- Complexity (MSE) of brain increases with growth, but not uniformly
- Multiscale complexity degrades with pathology/aging/toxicity

Normal
Controls

High risk
ASD

Preliminary
ASD diagnosis

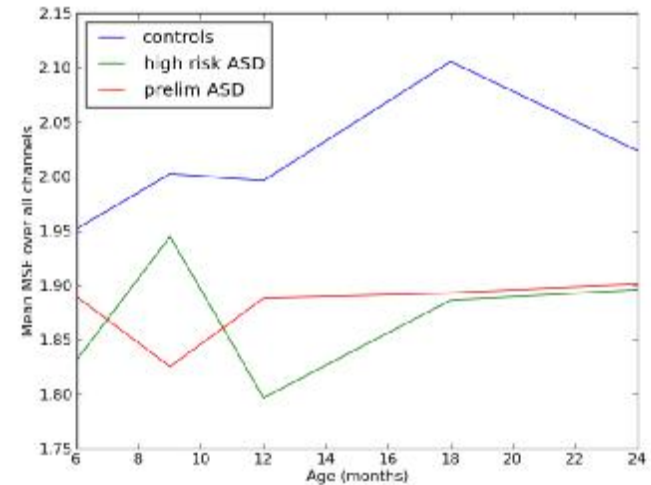
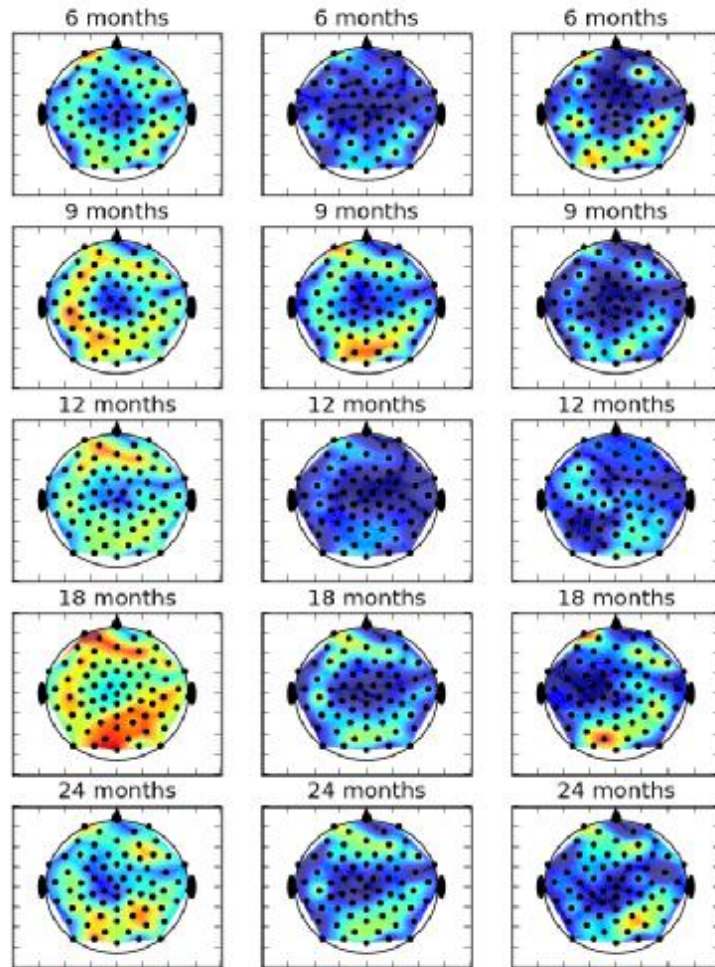
(19, 21, 1)

(13, 13, 3)

(26, 31, 1)

(6, 6, 3)

(3, 7, 1)



B.

Figure 1.

A. Mean multiscale entropy (MSE) at each channel. The number of subjects in each sub-group is shown to the left of each row.

B. The mean MSE over all channels is shown versus age. The general trend in the normal group is increasing complexity with age, while the HRA and preliminary ASD groups are relatively flat overall. The changes in MSE, however, are not uniform over all channels.



Summary: MSE

Multiscale entropy appears to be a promising approach to understanding complexity of EEG signal at a given age and across developmental time



Distal Goals

- Examining trajectories of development may be more informative than group differences in one slice of time (e.g., 6 months); for example,
 - When do we observe an inflection point in a specific domain (e.g., EEG gamma) that
 - distinguishes the high from low risk group?
 - predicts autism (as distinct from SLI, etc.)?
 - Does this inflection point correspond to what we might see in RNA expression data?²

² Both DNA and RNA are being collected on this sample, with the latter being collected at each test point along with our imaging measures



Distal Goals (Con't)

- Can we account for individual differences in our imaging data using underlying genetics (e.g., sort ERP data based on Copy Number Variants [CNVs])?
- How do we merge our imaging data and genetics data to derive a “profile” of individual children that ultimately
 - Predicts who does and does not develop the disorder
 - Distinguishes high risk/ASD- children from low risk/ASD- children?
 - Predicts response to treatment?



THE END