Early Assessment: Early Intervention
Imaging the developing brain

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Early Autism: Advances in Research and Clinical Practice

Yale School of Medicine, 12 April 2018

The authors have nothing to disclose.

Autism: Definition

- Persistent difficulties in communication
- Restricted, repetitive patterns of behavior
- Symptoms present in early development
- Significant impairment in functioning
- Not explained by intellectual disability

Autism: Neurologic phenotype

- **Persistent difficulties in language and communication**
- Restricted, repetitive patterns of behavior
- **Symptoms present in early development**
- Significant impairment in functioning
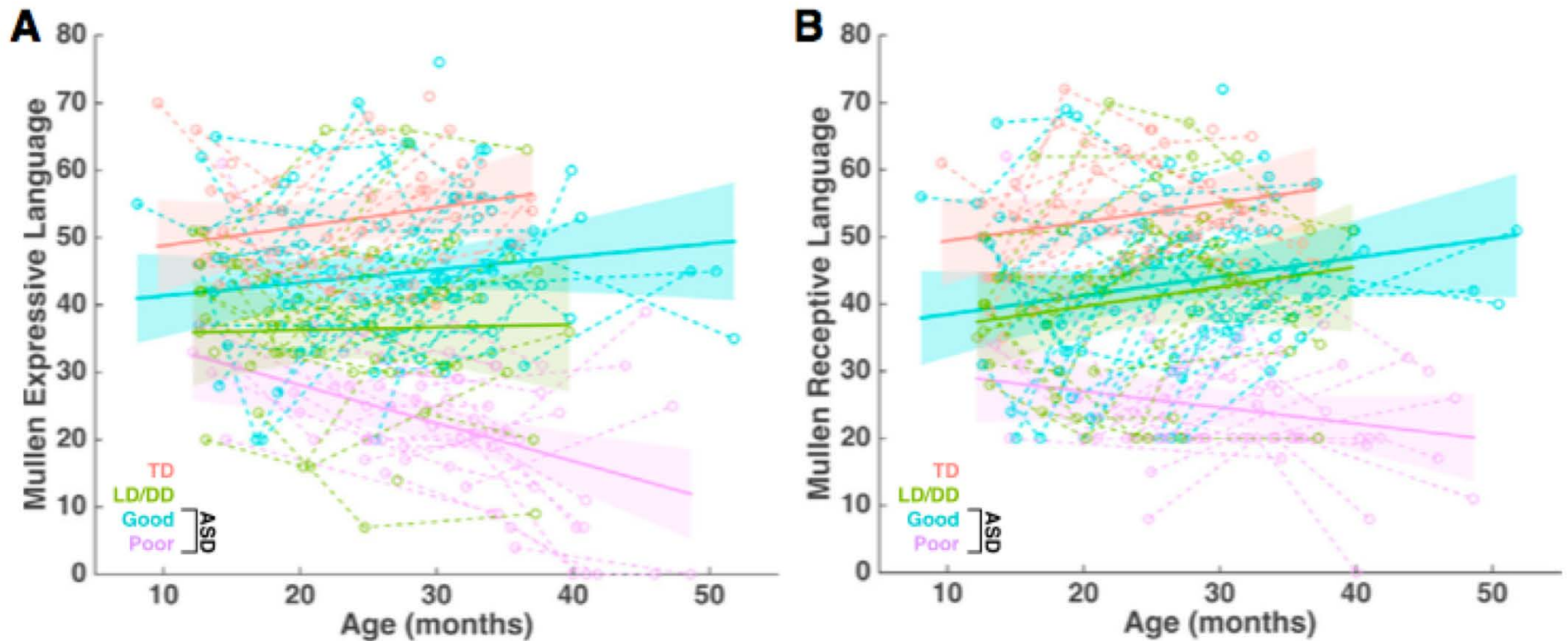- Not explained by intellectual disability

Outline

- Language difficulties are pre-programmed in children at risk for ASD

- Infants with CHD provide an excellent model

- Language systems are altered prior to birth

Is there a prenatal phenotype for ASD?

Language development is heterogenous in children with ASD

Lombardo et al, 2015

103 toddlers, ages 12-48 months, with serial language assessm

How to predict language outcome in young children at risk for ASD?

Lombardo et al, 2015

- 103 toddlers
  - 12-48 months
  - TD, ASD (good, poor), LD
- Resting state fMRI
  - Complex forward speech
  - Simple forward speech
  - Backward speech
- Pre-diagnosis fMRI predicted language outcome
  - In multivariate analysis with multiple predictive factors, fMRI was most sensitive
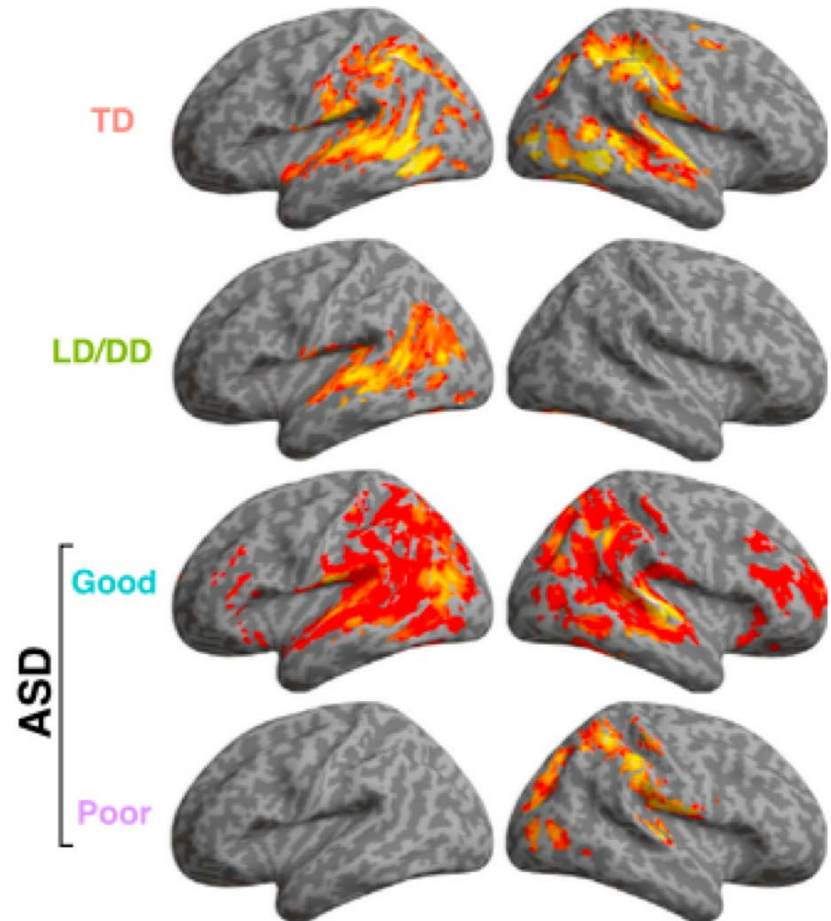
Neural networks for language are altered in some children with ASD prior to diagnosis

Congenital heart disease

## A genetic and neural systems model for ASD
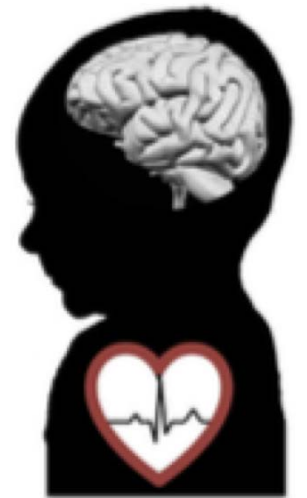
Infants with CDH:
High risk for both NDD & ASD

- Incidence of NDD 10 – 50%
- ASD: 4-5 fold increase
- Attributed to hypoxemia
- Genes contributing to cardiac develop also contribute to the connectome

White matter volume predicts language in toddlers with CHD

Rollins et al, 2017

- 48 toddlers – biventricular CHD
  - 13 healthy controls
  - 12 months
  - MacArthur Bates Communicative Development Inventory
- Volumetric MRI studies
- CHD vs controls
  - Decreased WM
- For CHD children only
  - White matter volume correlated with language development
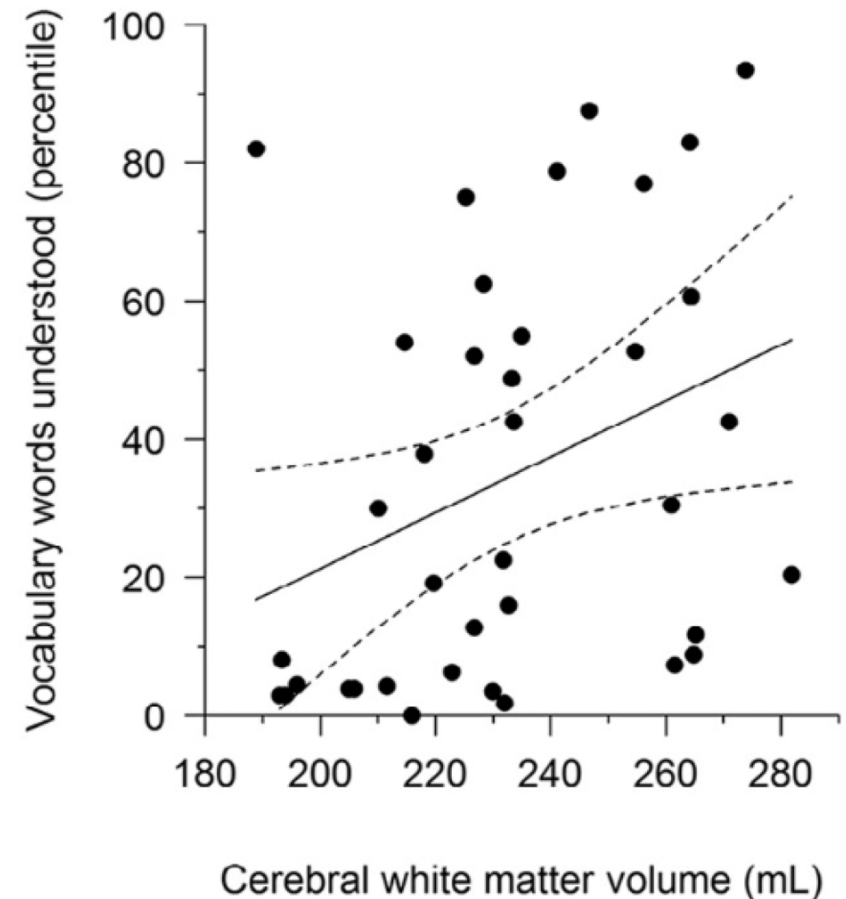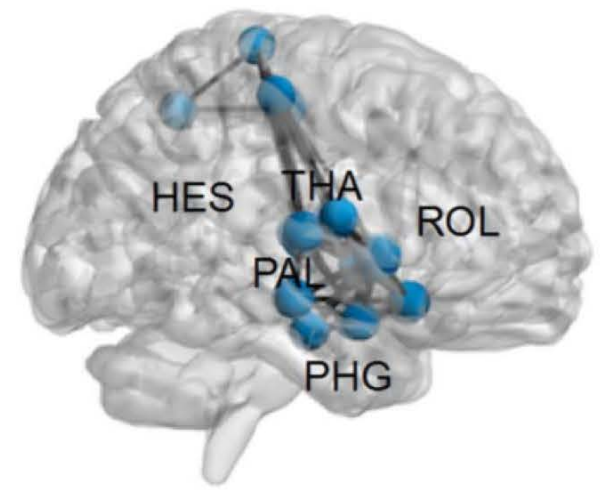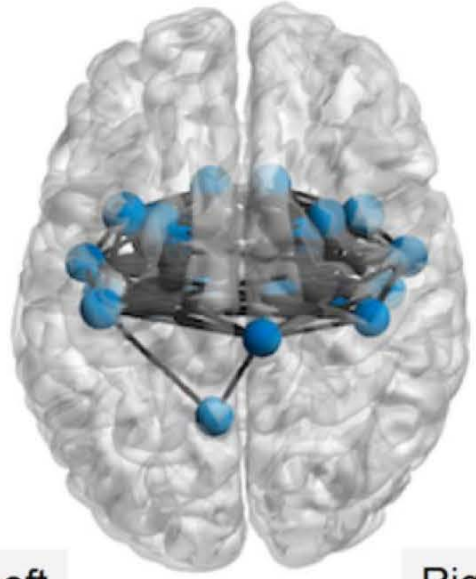
Aberrant connectivity in newborns with CHD before surgery

De Asis-Cruz et al, 2017

- CHD infants are at risk for hypoxemia
- Hypoxia alters neural connectivity
- 30 CHD before surgery + 32 controls
- Resting state fMRI
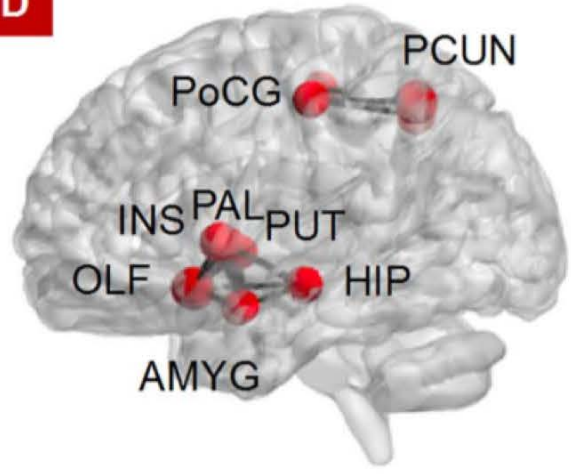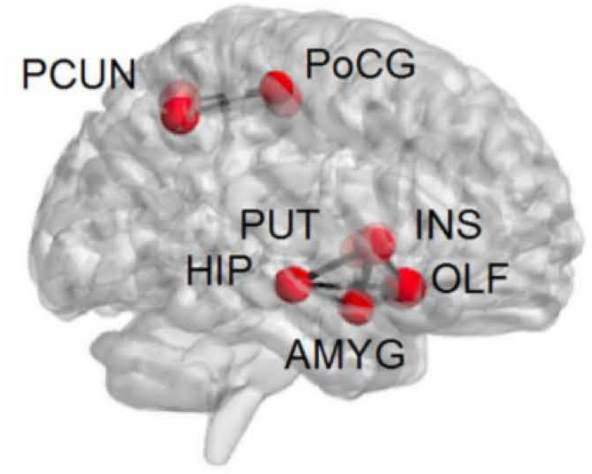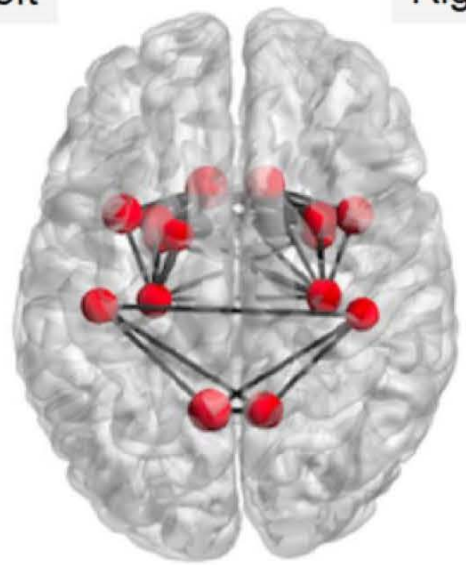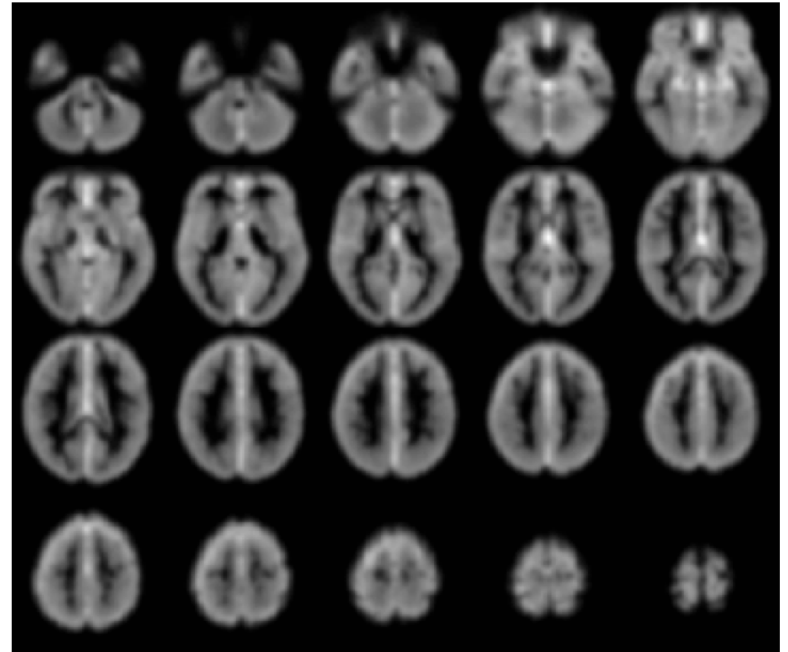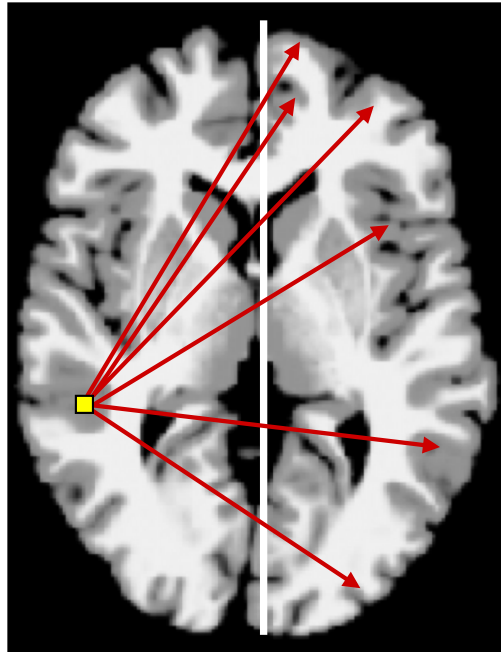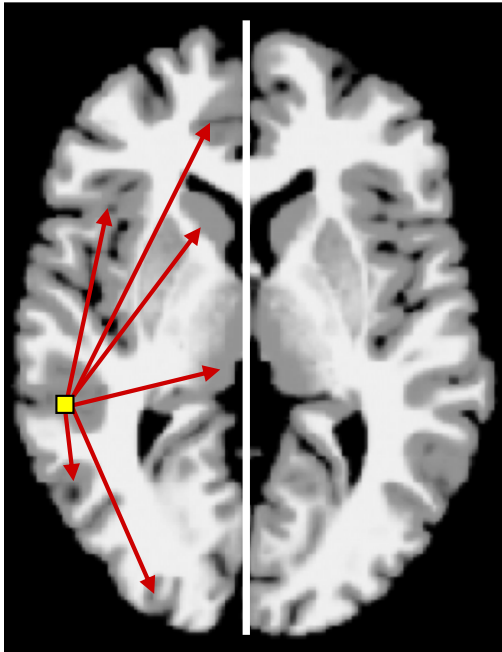 - Intact global topology
  - Reduced regional connectivity
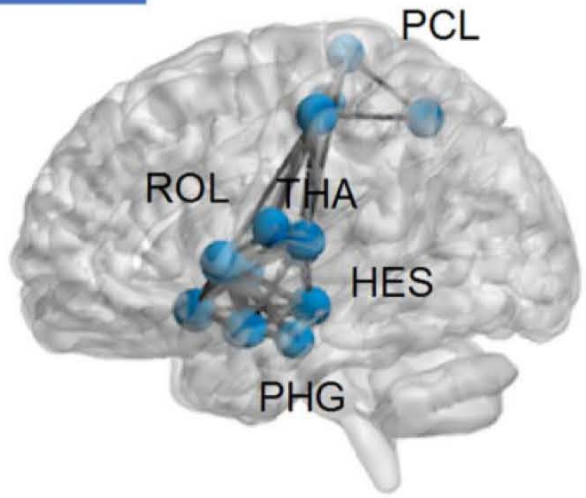
The nodes are there; they aren't all connected.

Alterations in language networks are present prior to hypoxemia in infants with CHD

Preterm-born children

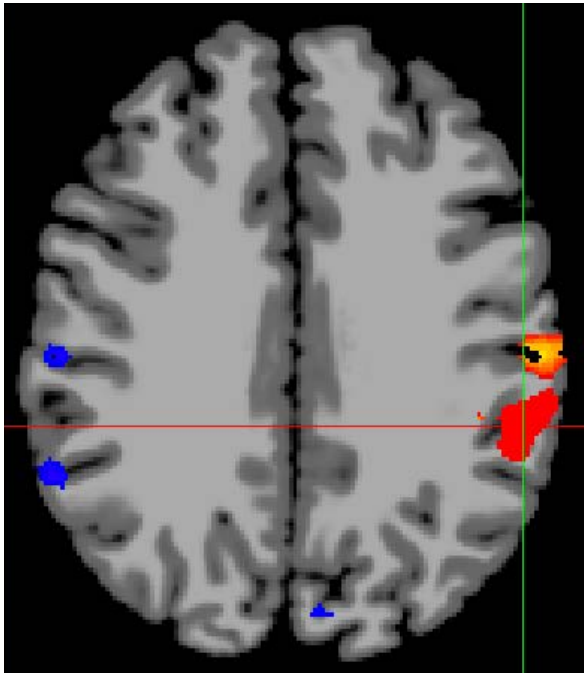## High risk for language disorders and ASD

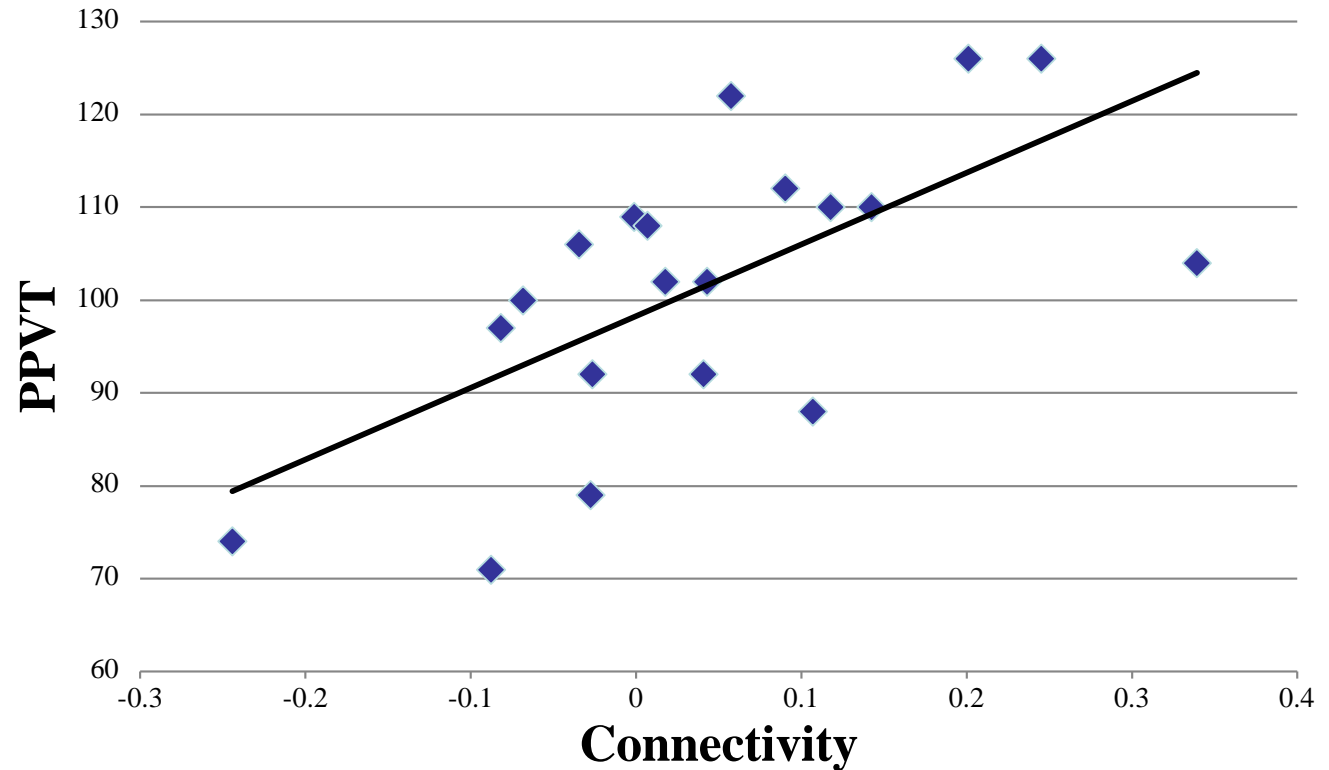# Voxel-based resting state connectivity lateralization

Ipsilateral - Contralateral = Connectivity lateralization

Lateralization for language makes humans unique

Compared to term controls,
Preterms have less lateralization in L BA22
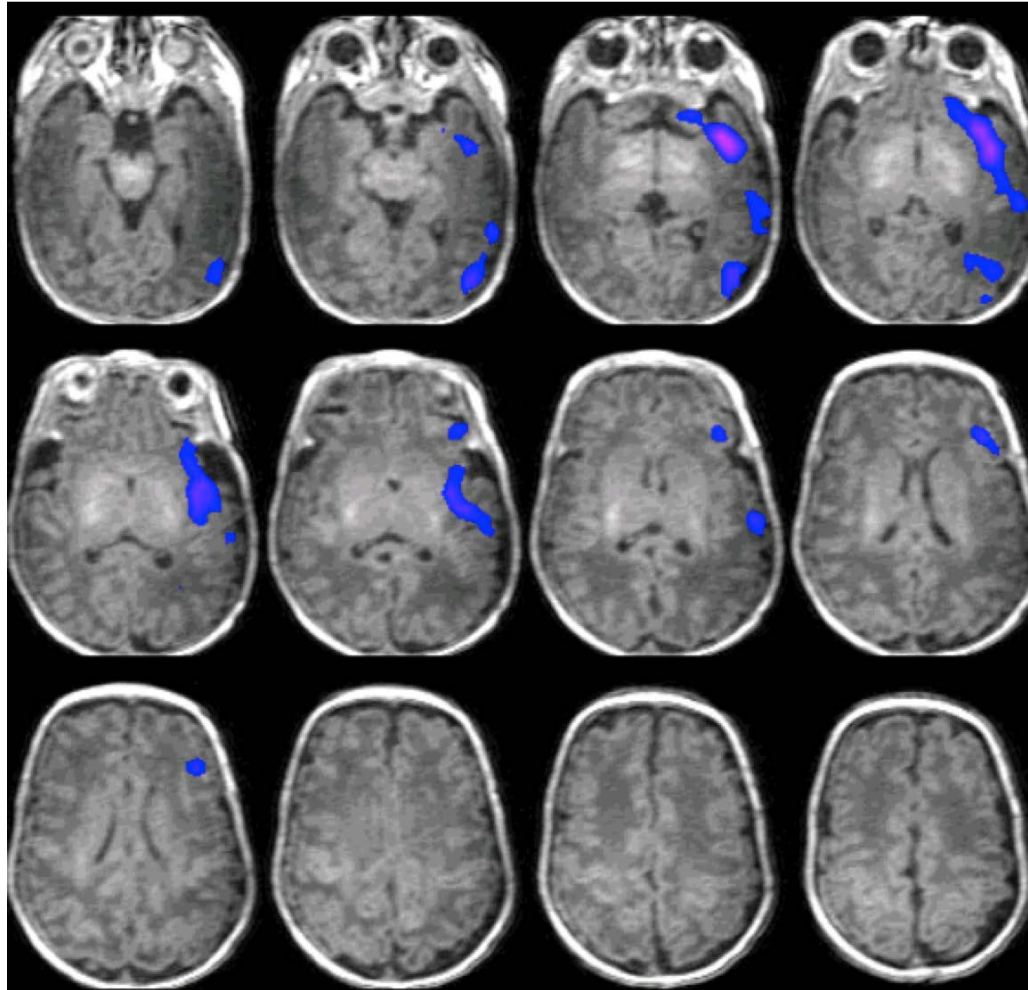

T – PT, age 16 yrs

r=0.65 p=0.002

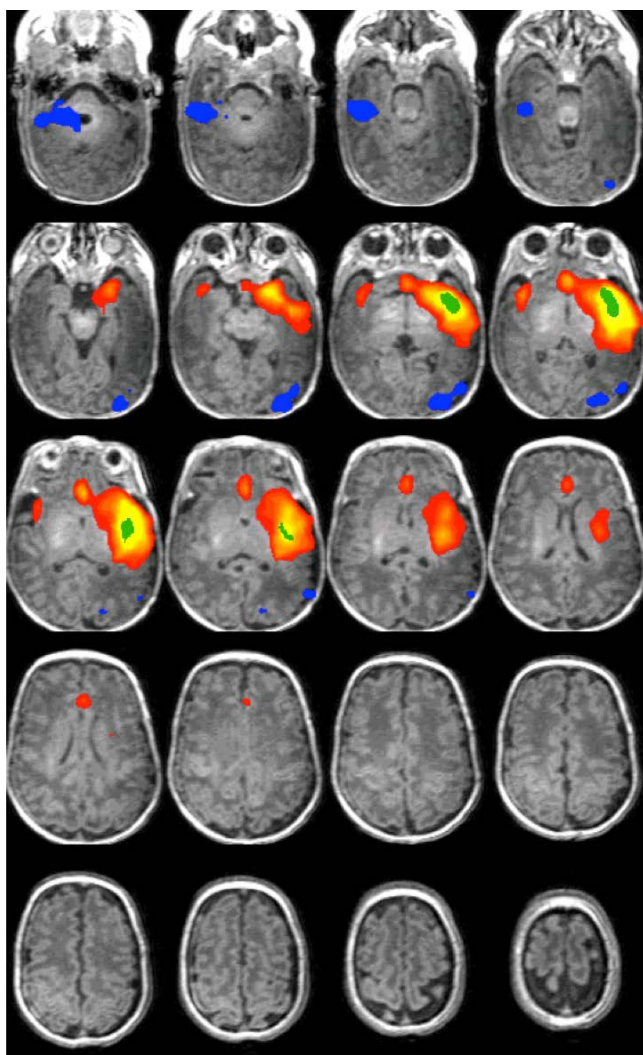Better scores with left lateralized connectivity

What about neonates?

Preterms don't lateralize for language

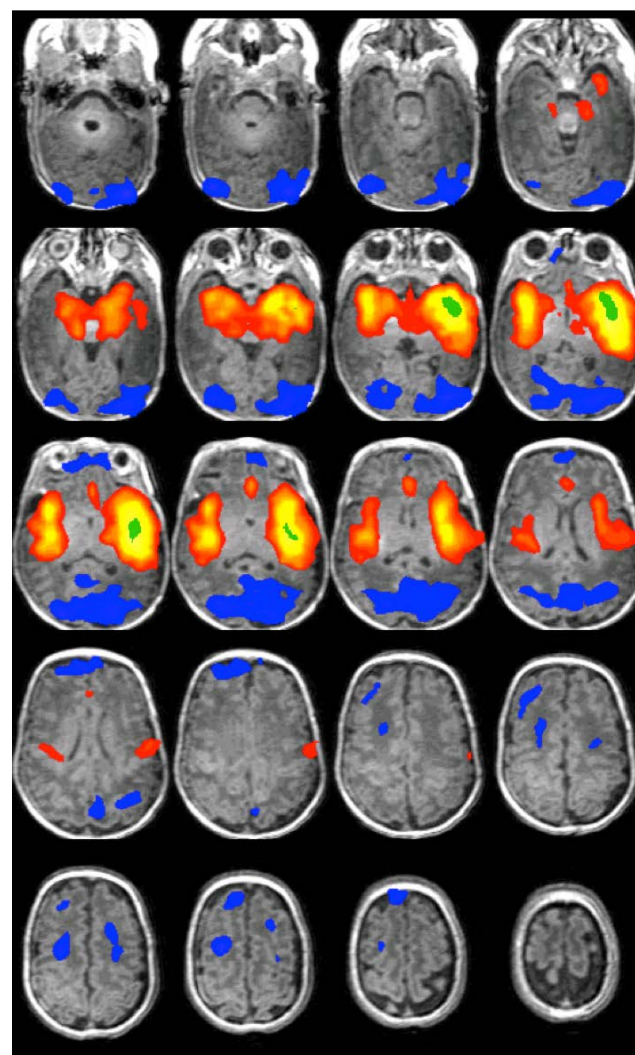26 PT neonates < 28 wks GA, 25 controls, p < 0.001

Preterms don't connect to homologue of L BA22

Preterm

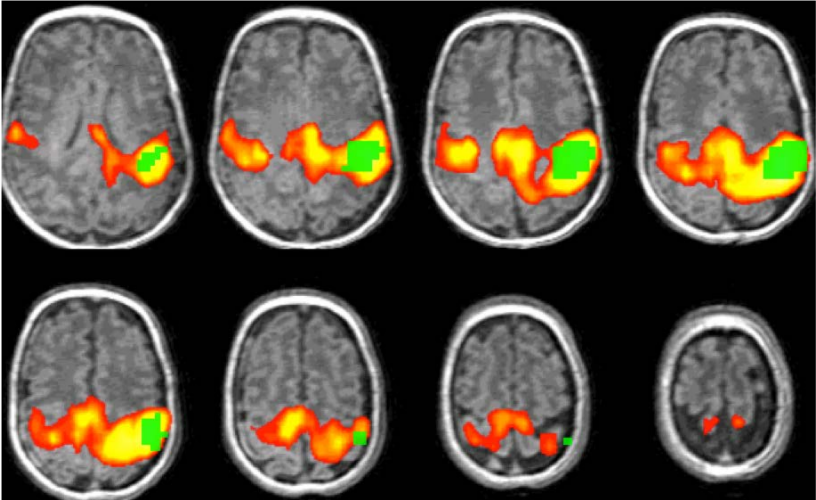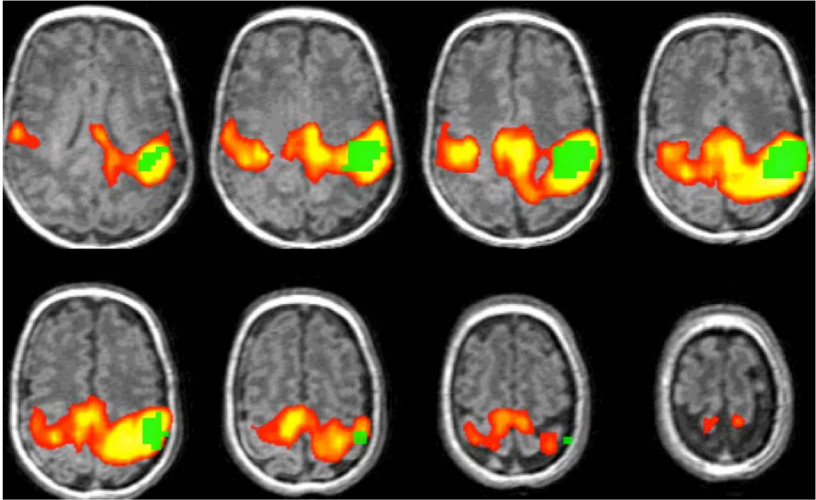Term controls

* p < 0.001

Preterms connect to homolog of motor cortex

Preterm

Term controls
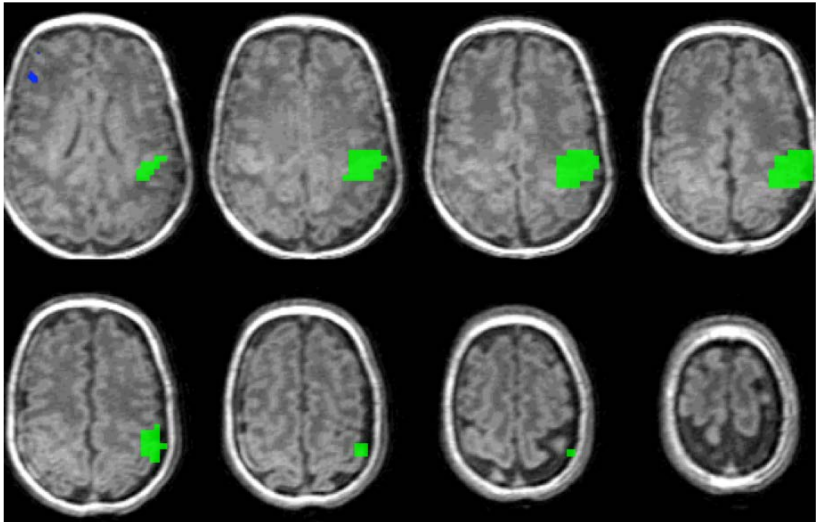
Kwon et al, 2014

How to investigate these findings?
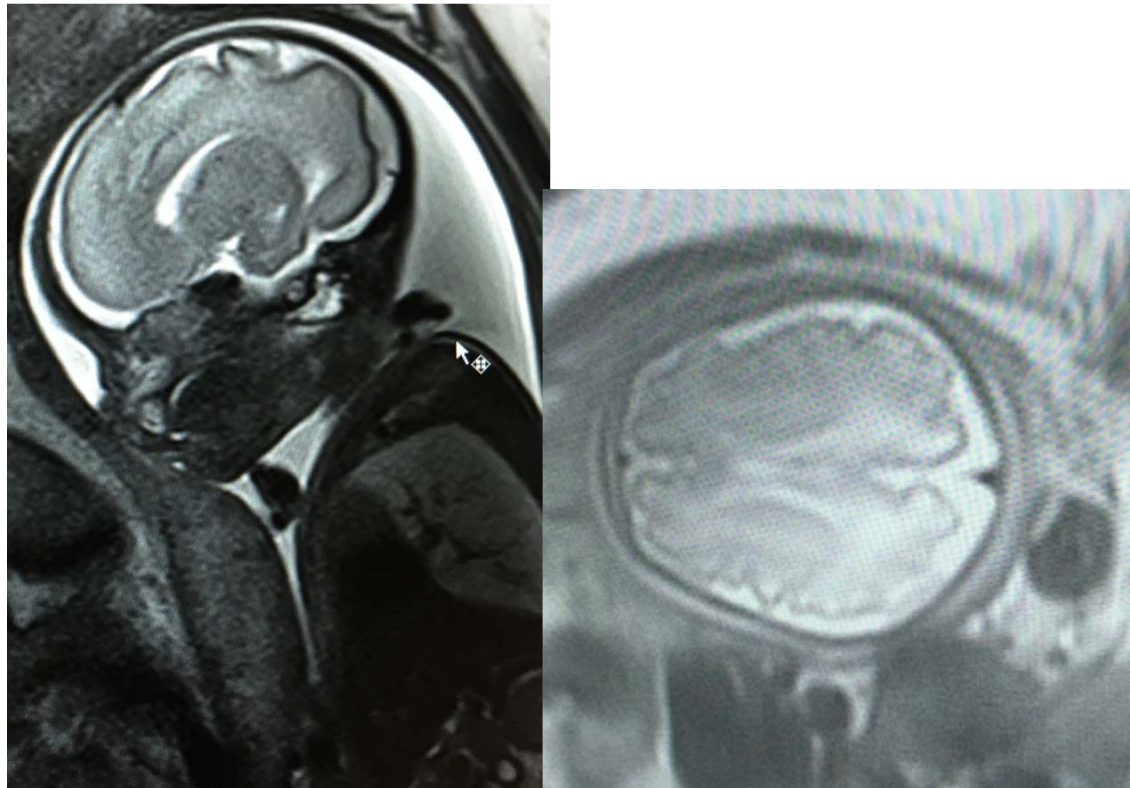
Fetal lateralization at 30 and 34 weeks GA

30-32 wks GA

34-36 wks GA

p=0.05   p<0.001
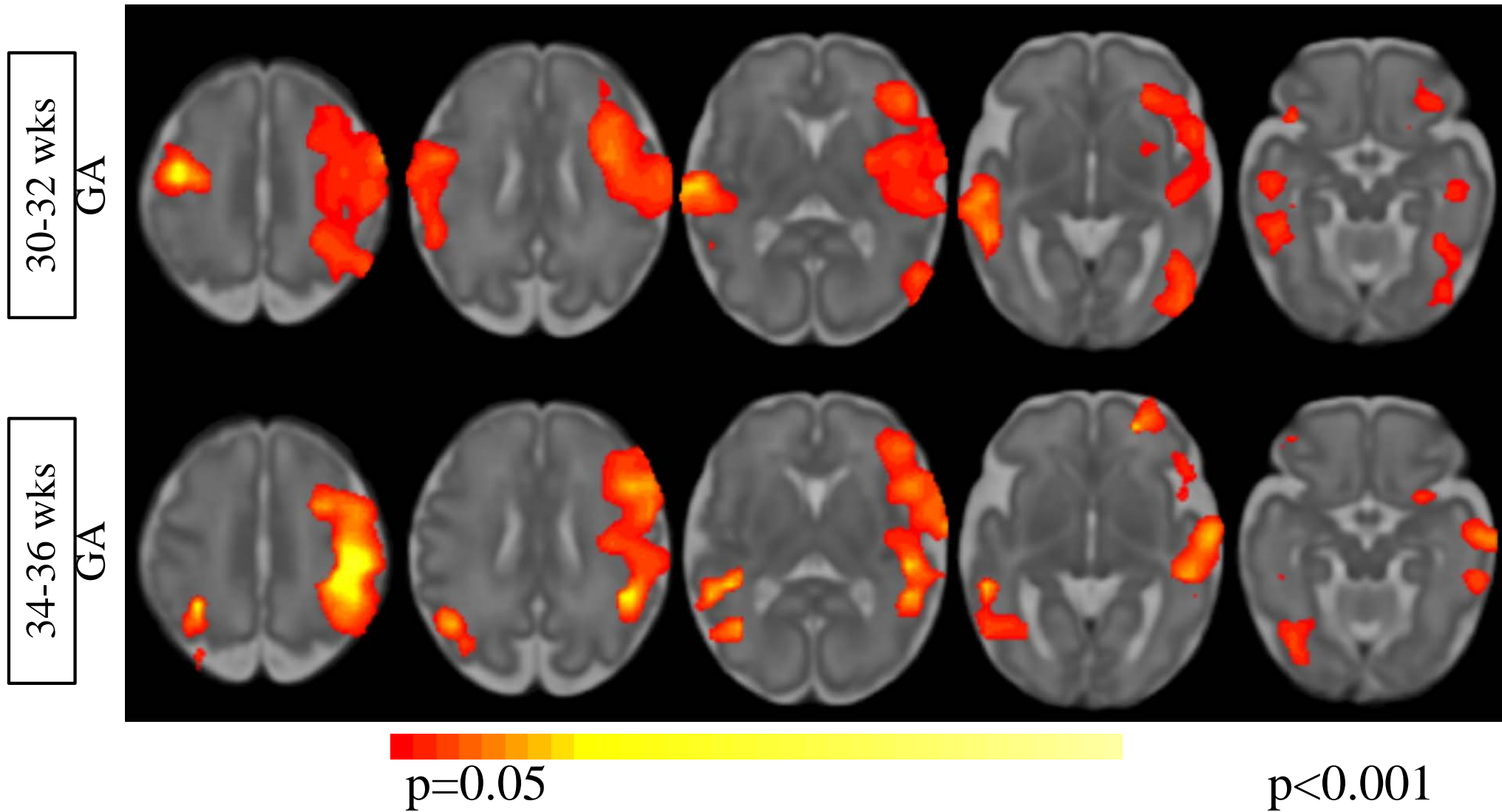
Is the preterm language syndrome present before birth?
Thomason et al, 2017

- 32 women with AGA fetuses
  - Fetal resting state functional MRI
  - Mean GA 29 weeks; range 22 – 36 weeks
- 14 pregnancies ended in preterm delivery
  - Mean GA 32 wks; range 24 – 35 weeks
- 18 uncomplicated term pregnancies

Alterations in language systems in the PT brain before birth
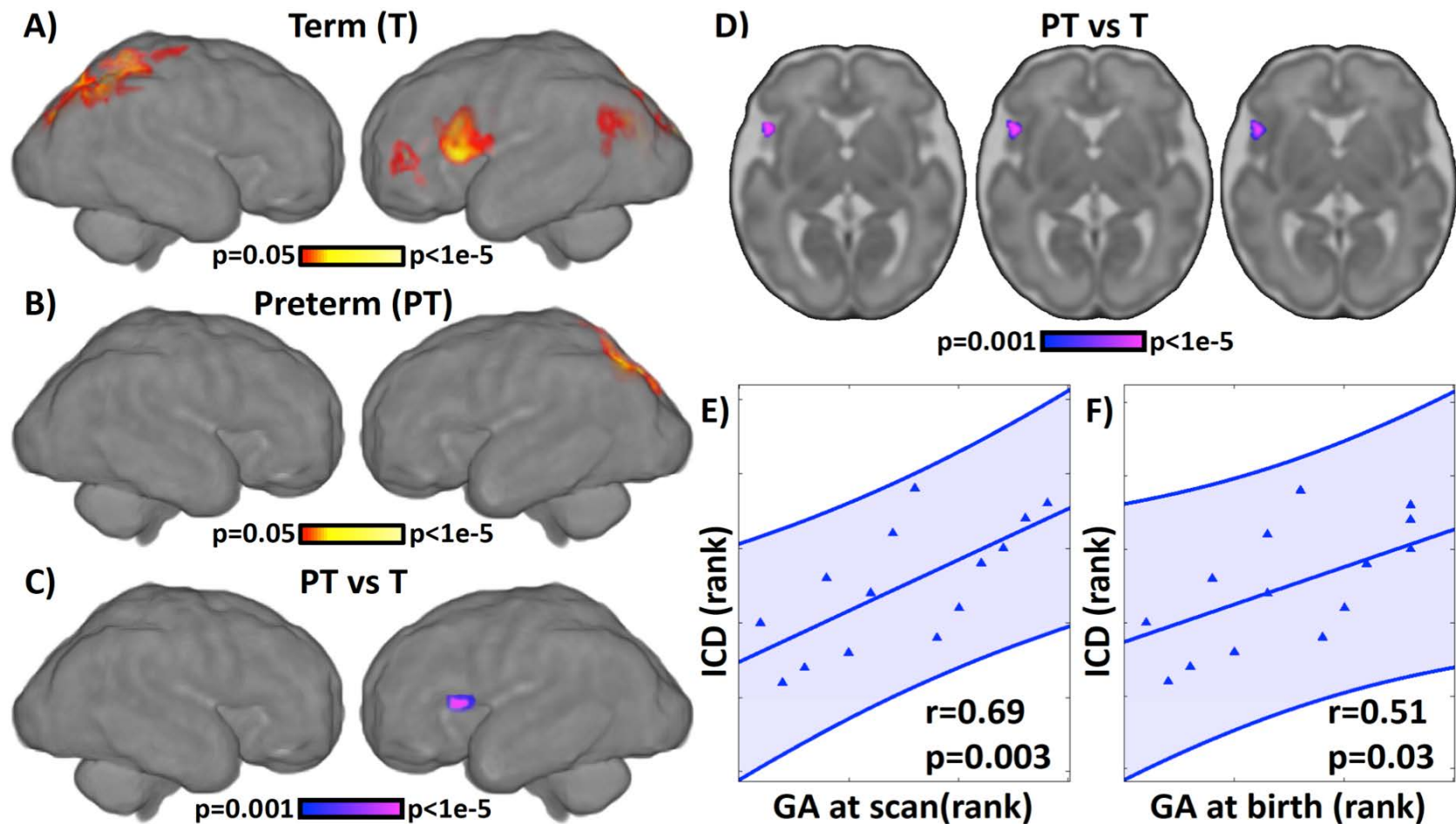
Connectivity predicts PT birth

PT: Correlation between seed connectivity and GA(birth-scan)

A)

p=0.05 p<1e-5

B)

Seed (rank)

r=0.75
p=0.002

GA(birth-scan) (rank)
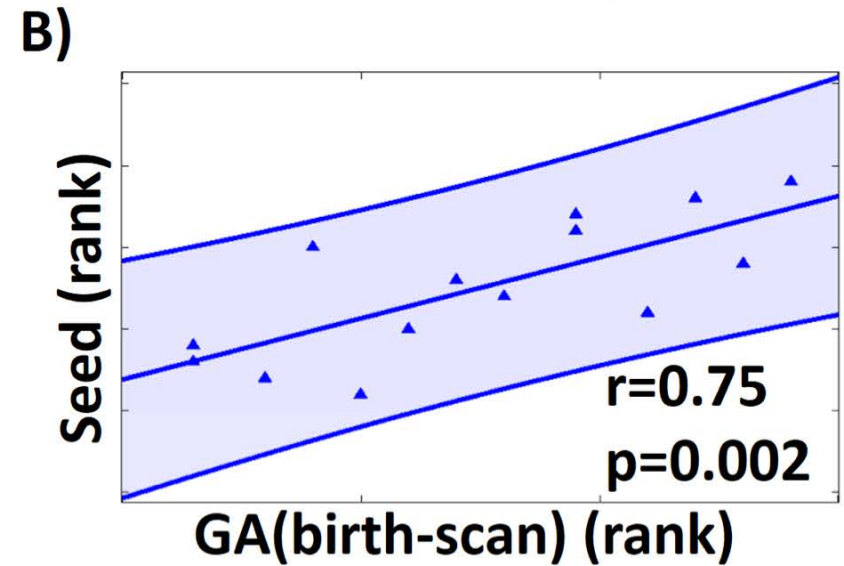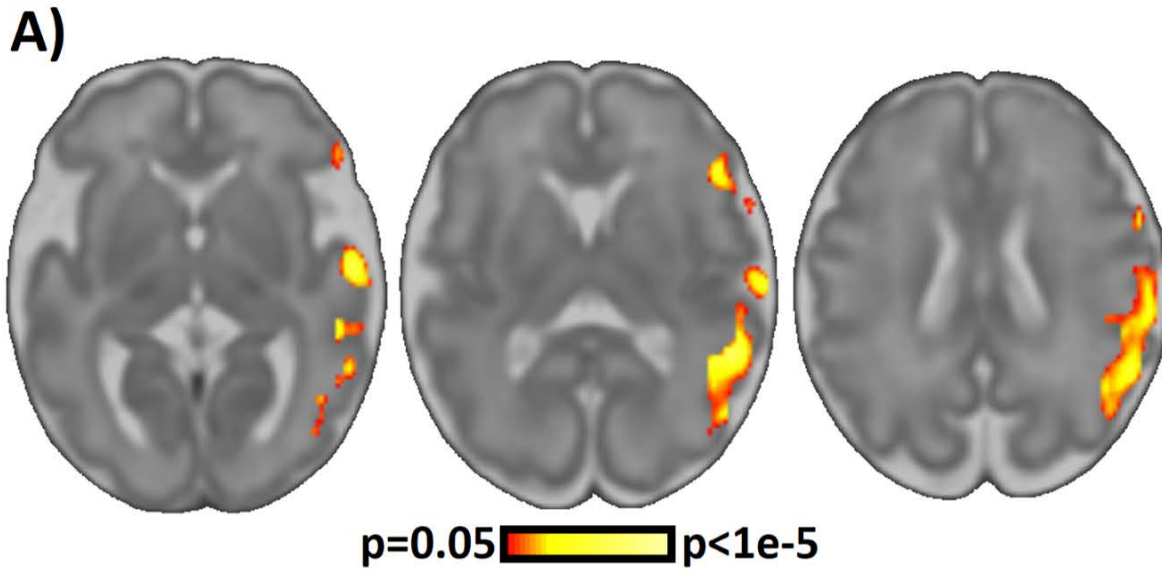
Alterations in language systems are present before birth

Proposal
Very early intervention

Songbirds:
Very early intervention

- Excellent model for vocal learning
- Electrophysiology, histology, molecular mapping and fMRI studies
- Ante- and postnatal learning paradigms
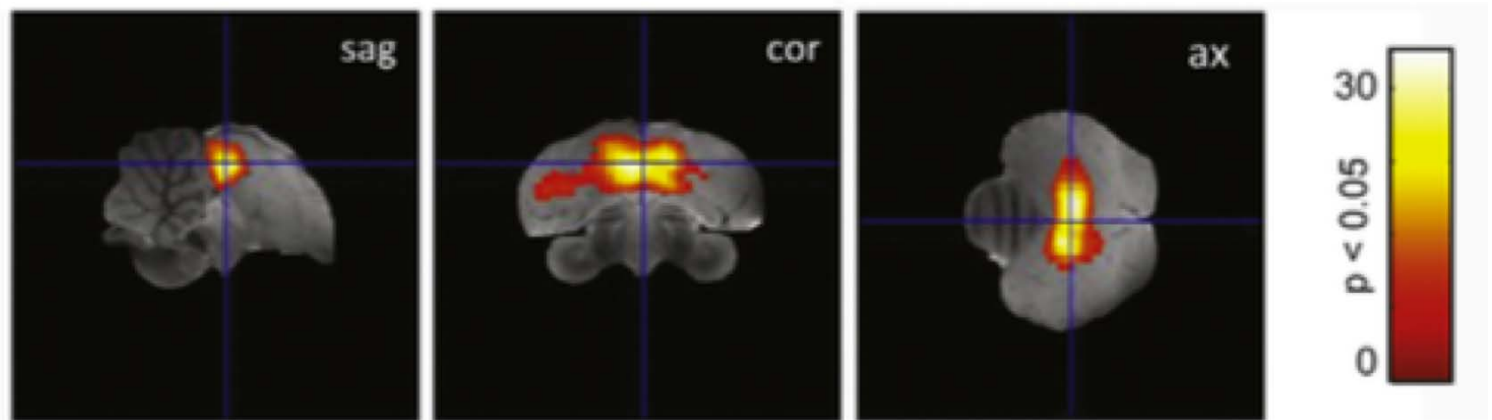
Van Ruijssevelt et al, 2013

Birdsong: Fetal intervention

- Markham et al, 2008

- 118 Bobwhite quail embryos
  - Early, mid- or late gestation exposure to Bobwhite or scaled quail maternal calls
  - Auditory & visual assessment

- Mid-gestation exposure: prefe calls to which exposed

- Late gestation: Bobwhite calls

Language experience in utero affects vowel perception after birth

Moon et al, Acta Paediatrica 2013

- 80 newborns
  - 40 in Stockholm
  - 40 in Seattle
- Mean age 33 hrs
- Audio presentation of native or non-native vowels
  - Assessed by number of sucks
- Increased sucking to novel vowel sounds
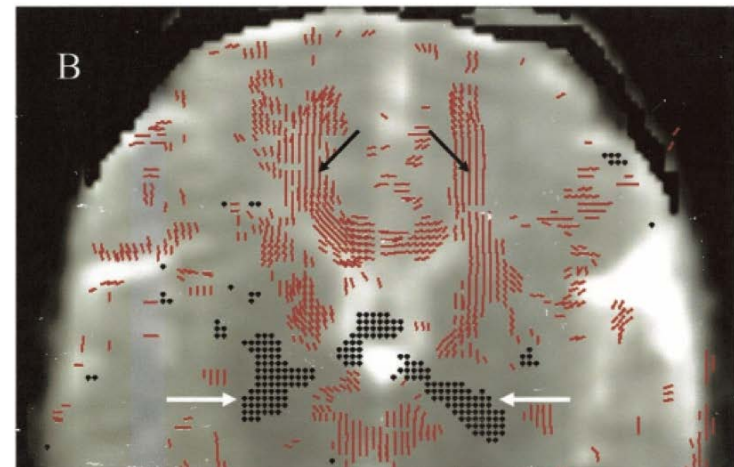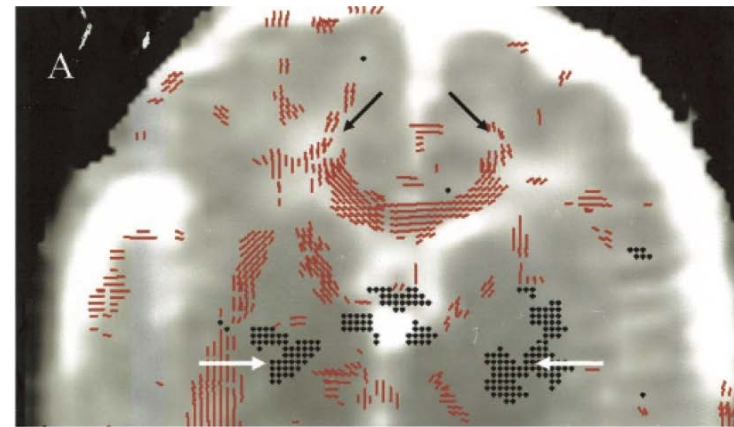 - Fetuses are listening

Video courtesy of Hugo Lagercrantz, MD, PhD

Early experiences alters structure and function

Als et al, 2004

- RCT
  - 30 PT neonates
  - 28 – 33 weeks
- NIDCAP 72 hrs to 2 weeks vs routine care
- Experimental vs control:
  - MRI at TEA: increased micro-structure in internal capsule & frontal WM
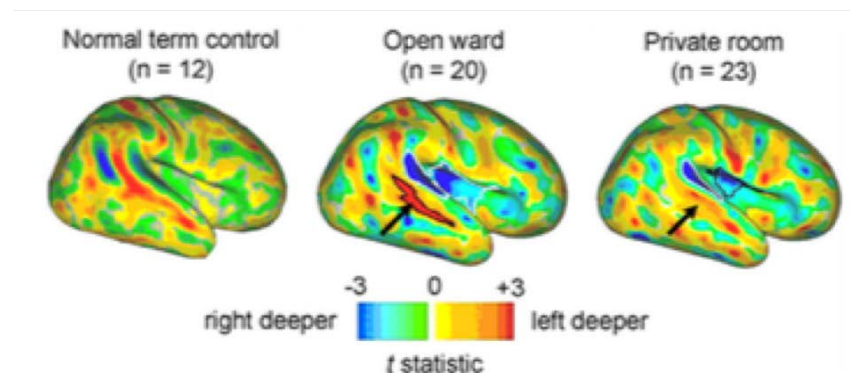 - Neurobehavior improved

Experience-dependent plasticity

Talk to your baby
Language in the prematurely-born

- ## Caskey & Vohr, 2011
  - Exposure to parental talk in the NICU was a strong predictor of language outcomes

- ## Pineda et al, 2014
  - PT infants in private rooms had less hemispheric asymmetry & lower language scores

- ## Webb et al, 2015
  - PT infants randomized to maternal language had larger auditory cortices than controls

Normal term control (n = 12) Open ward (n = 20) Private room (n = 23)

-3   0   +3

right deeper   left deeper

t statistic

Learning induced neural plasticity of speech processing before birth

Partanen et al, PNAS 2013

- ## 33 newborns
  - 17 learning; 16 controls
- ## 8 minutes/day from 29-40 weeks GA
  - 2 Conditions: TATATA vs TATOTA; pitch changes
- ## EEG assessment – mean age 4 days
- ## Learning group recognized vowel and pitch changes > controls ($p < 0.05$)
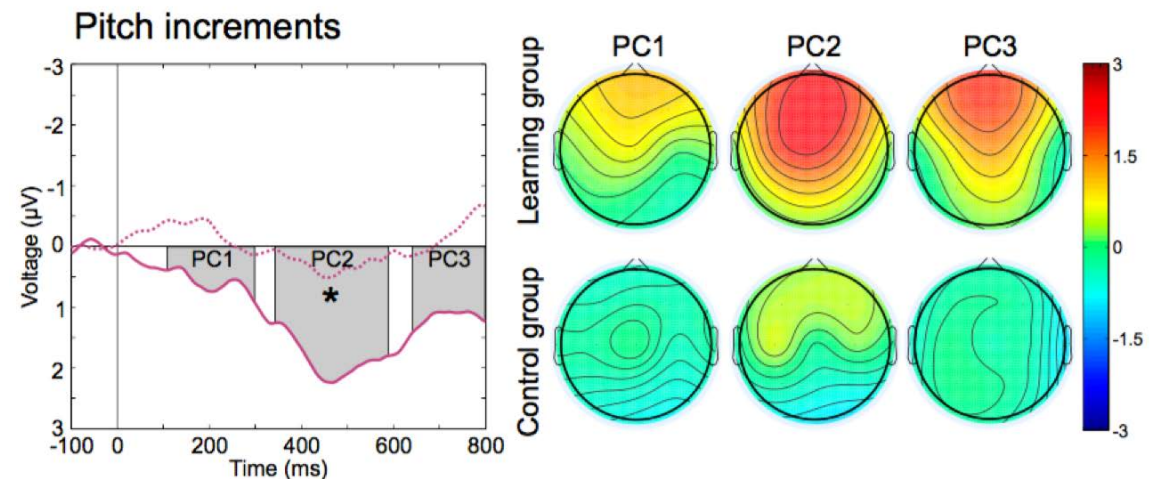
Conclusions

- Prenatal phenotype for ASD
  - Alterations in language systems

- Present during 2nd and 3rd trimesters of gestation
  - Role of genetics and epigenetics

- Language is malleable
  - Role of very early intervention
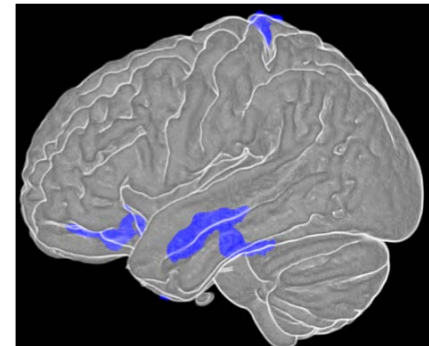
Thanks!

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200

100 YEARS *of* WOMEN

at Yale SCHOOL OF MEDICINE