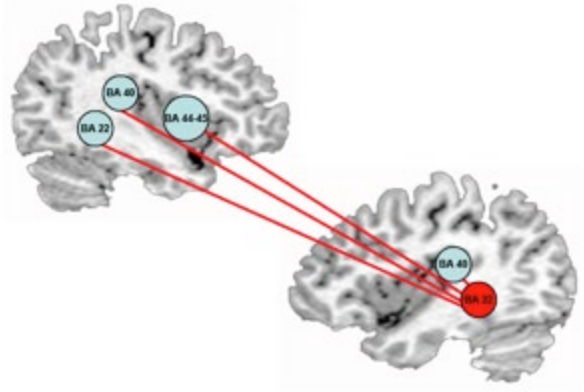

Language, lateralization and the developing brain

Models for ASD

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Yale School of Medicine

11 July 2019

The authors have nothing to disclose.

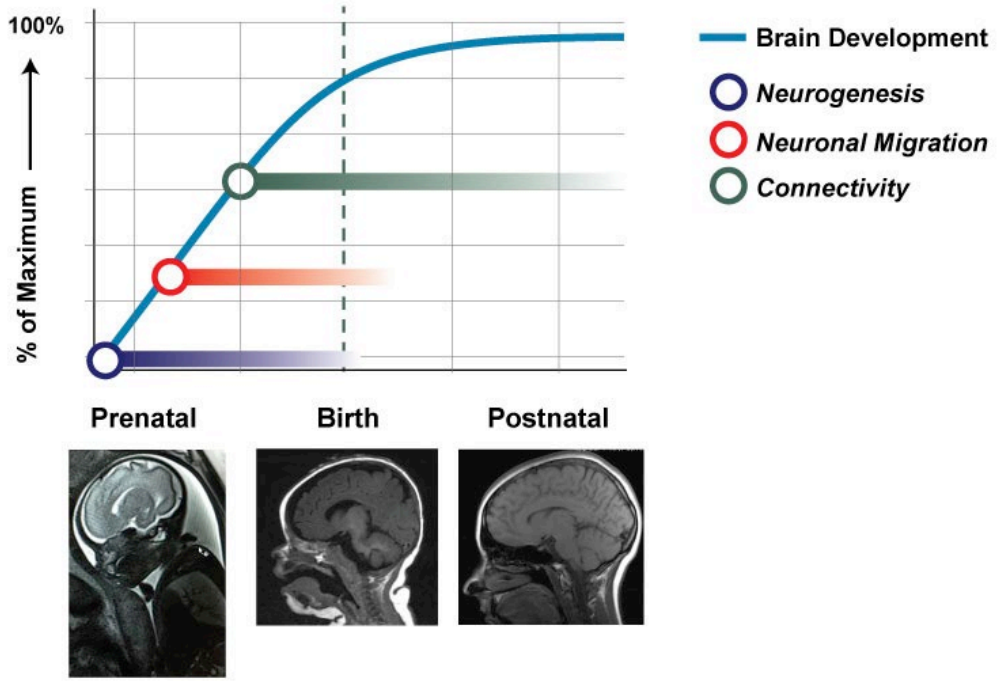
Definition 1

Autism - Neurological 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

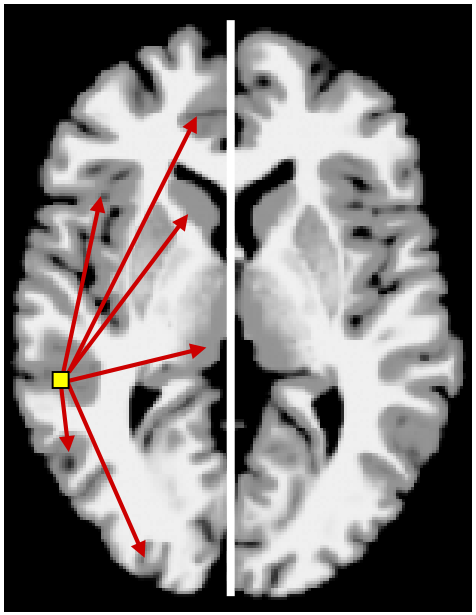
Definition 2

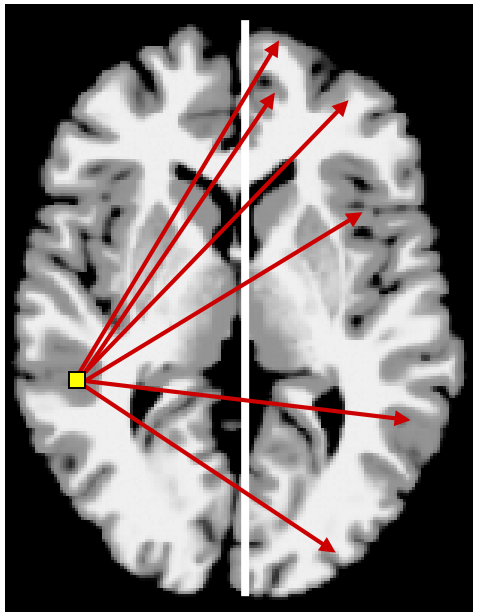
- "Neural connectivity is the intermediate between molecules and language."
  - O. Sporns, 2014

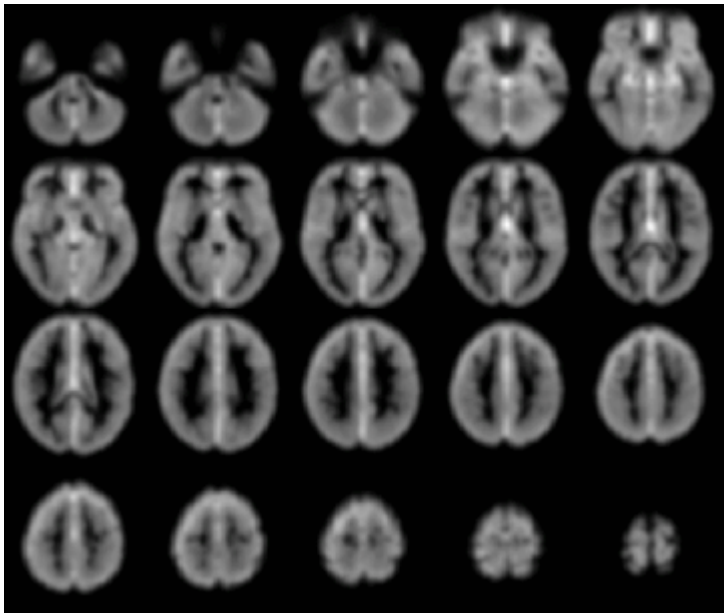


Adapted from Lussier, 2016

Definition 3
Lateralization







Ipsilateral - Contralateral = Connectivity lateralization

- Defining characteristic of human brain
- Localization of a given task to a specific region of the brain
- Correlated with language measures at school age, adolescence and beyond

Models for ASD

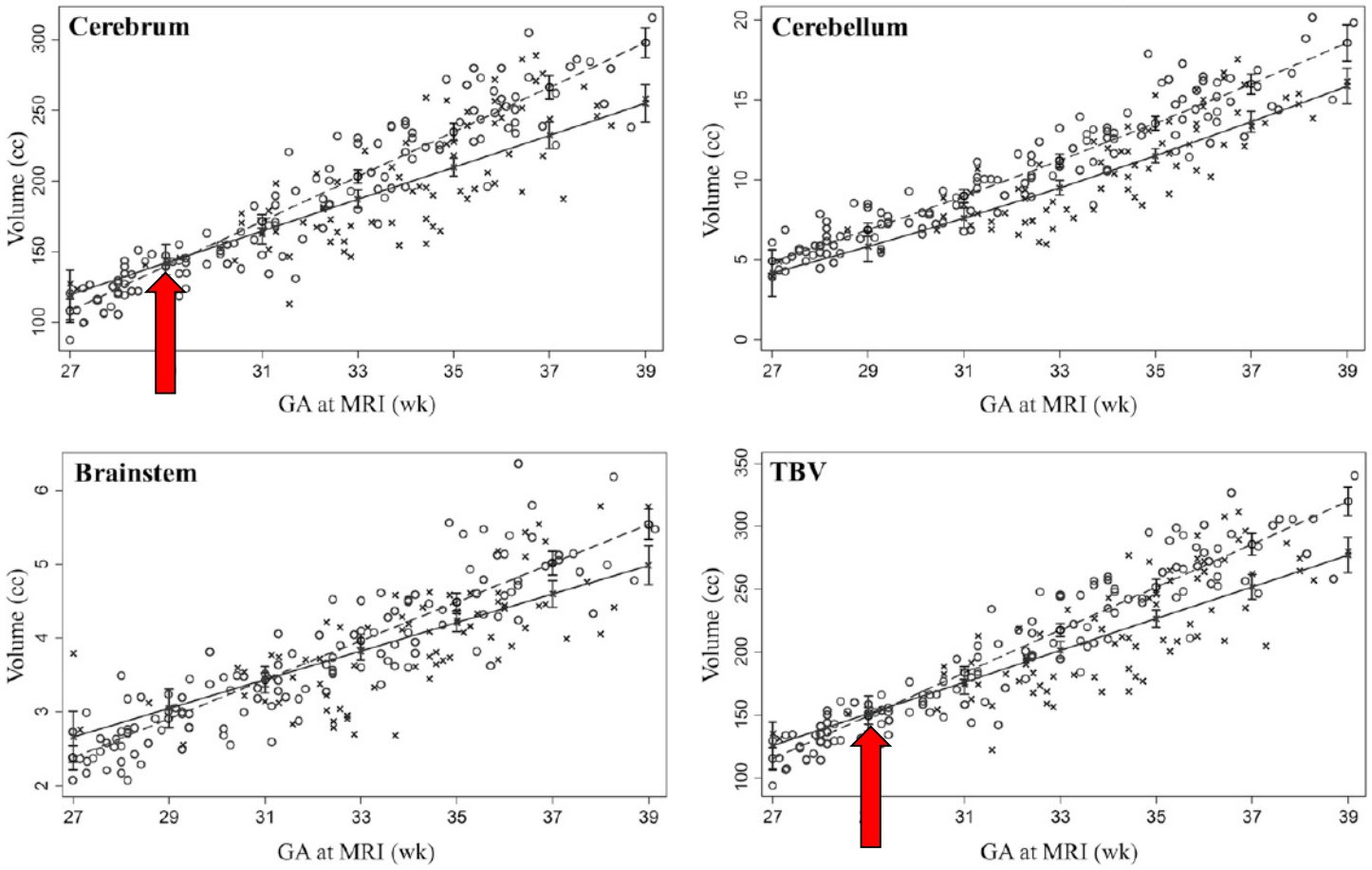
- Preterm-birth neonates
  - Environmental perturbation
- Children with congenital heart disease
  - Genetic variation

Preterm neonates

- High risk for language difficulties
  - Over 50% of PT < 28 weeks GA have phonologic processing disorders
  - 20% experience executive function difficulties
  - 7% are diagnosed with ASD

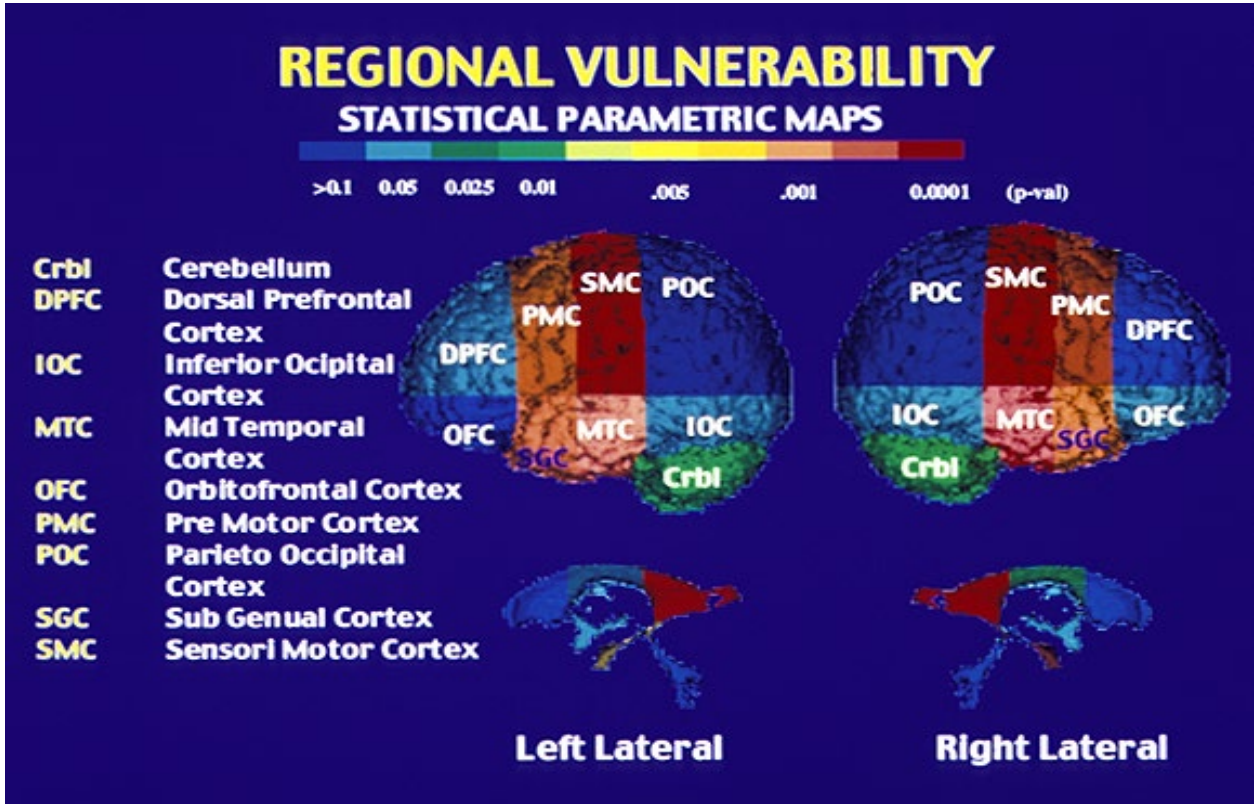
Preterm neonates also have poor brain growth

Limperopoulos et al, 2016



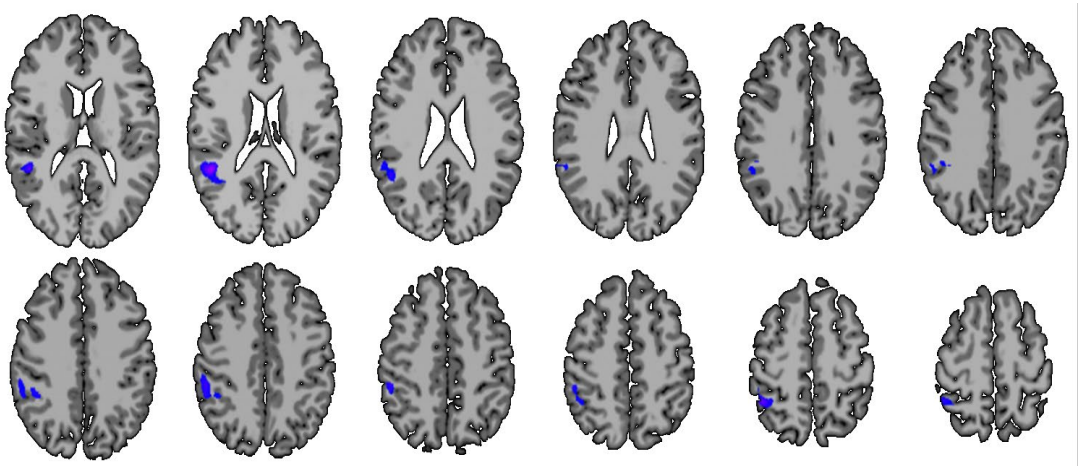
75 PT neonates with no brain injury; 130 fetuses

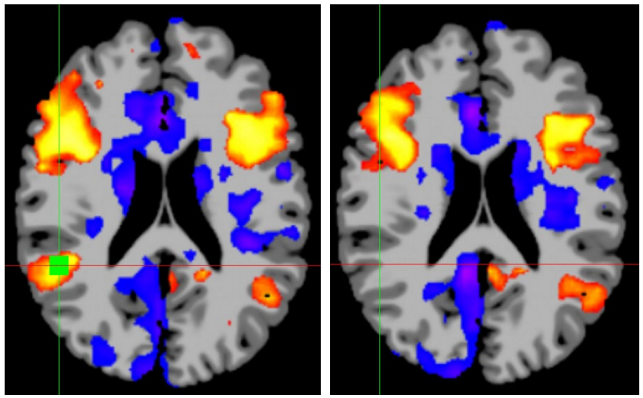
Language regions are vulnerable in the prematurely-born



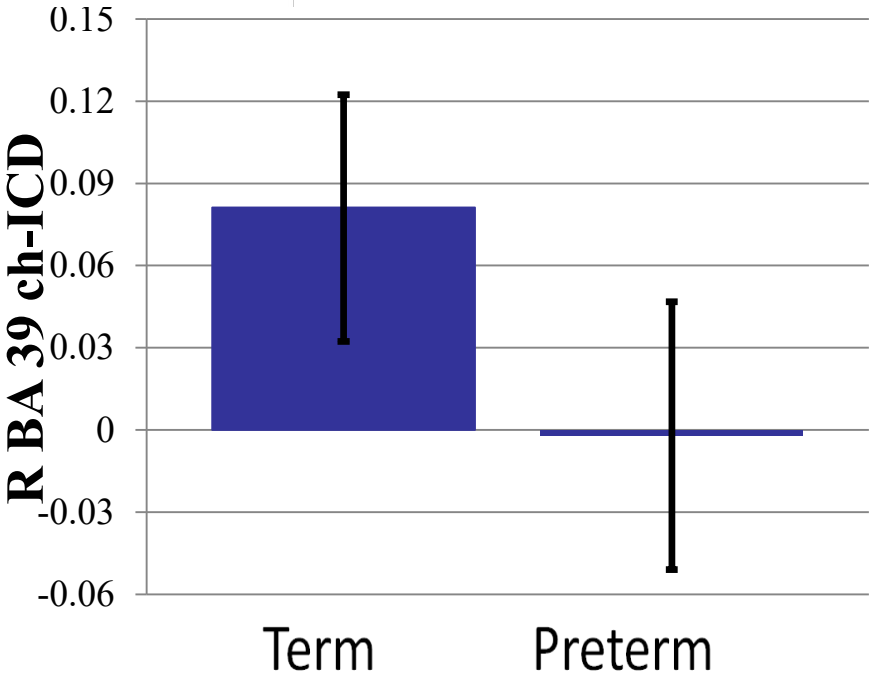
Peterson et al, JAMA 2000

Preterms have less lateralization for language at adolescence

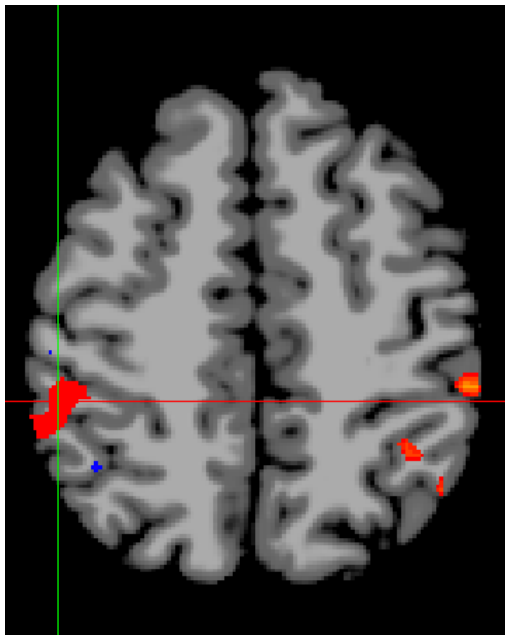


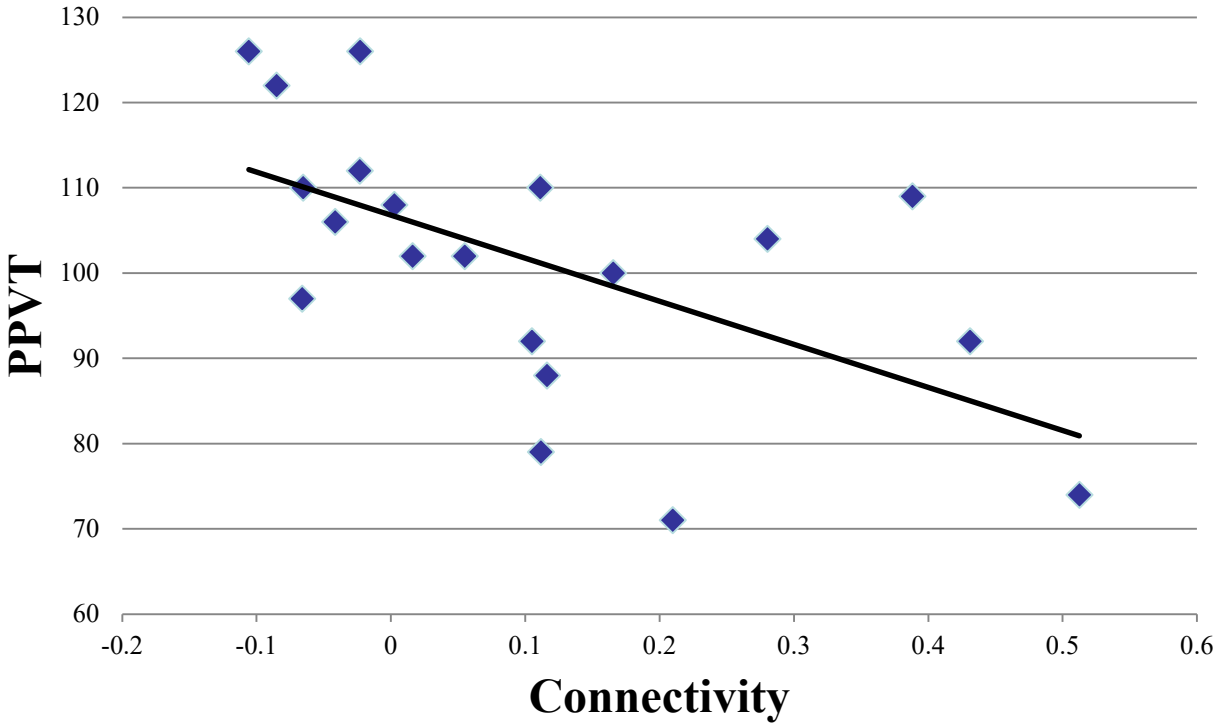


Term Preterm



R BA 40: Poorer scores with right lateralized connectivity



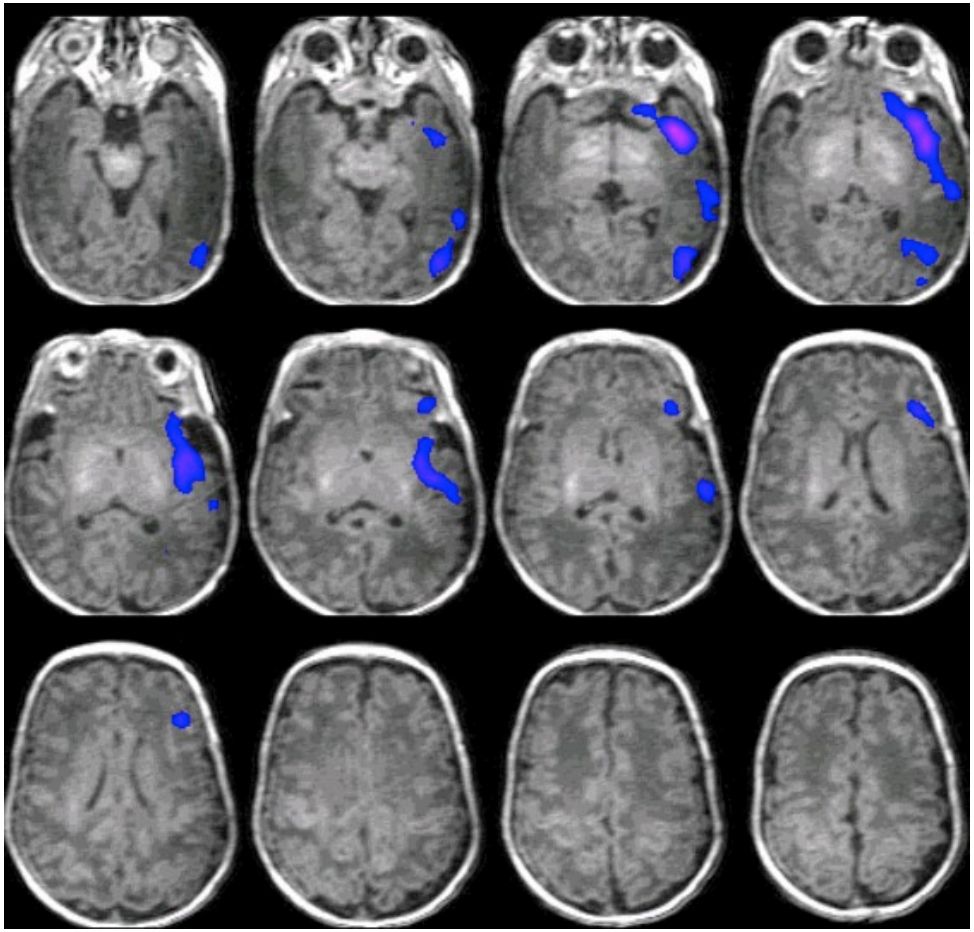


r=-0.58 p = 0.007

Preterms look less like terms

Scheinost et al, 2014

Preterms don't lateralize for language at term equivalent age

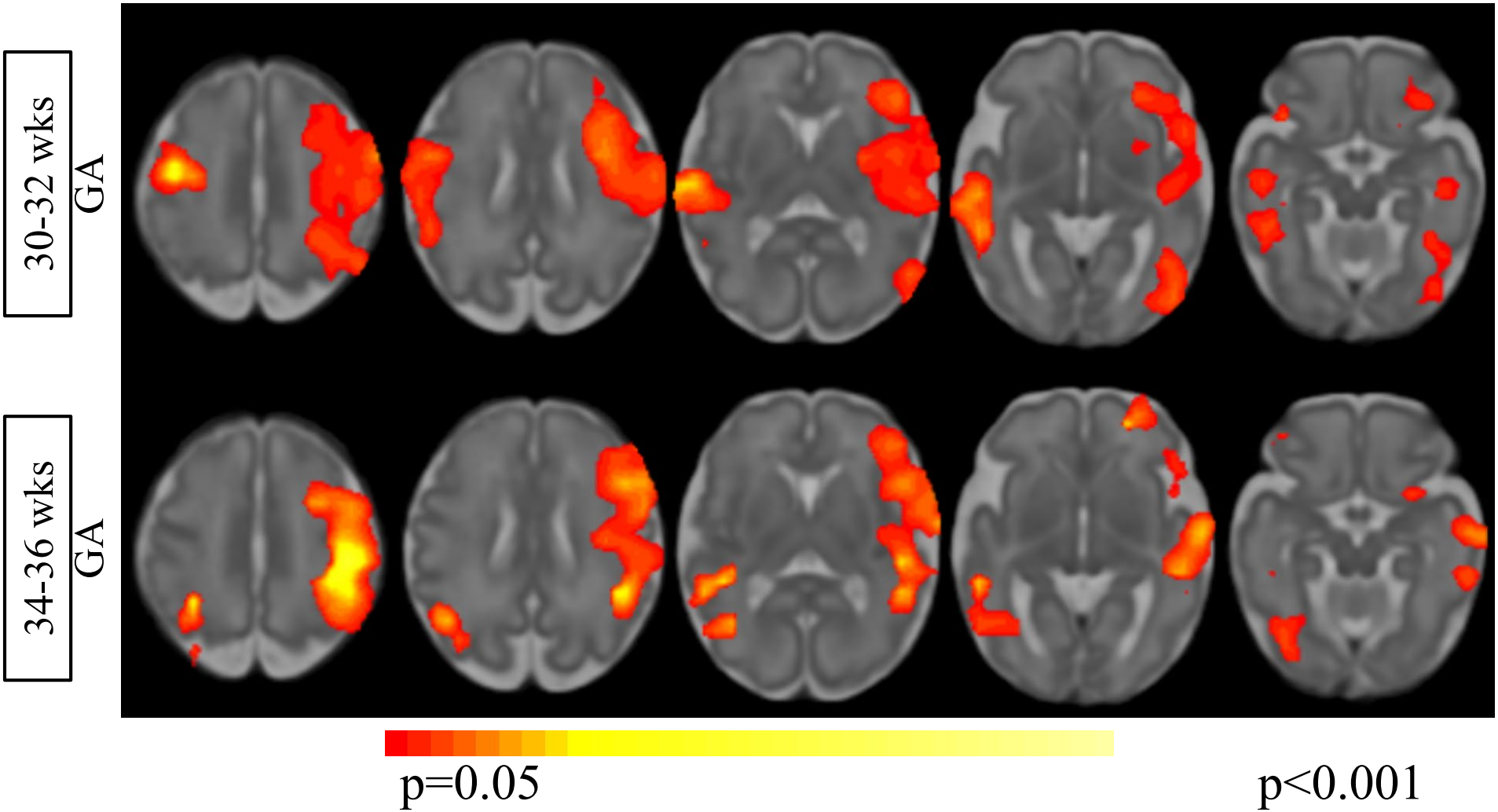


Lateralization is highly predictive of BSID III at 1 yr CA (p=0.007)

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

Fetuses lateralize at 30 weeks GA

ACE will tell us what this means

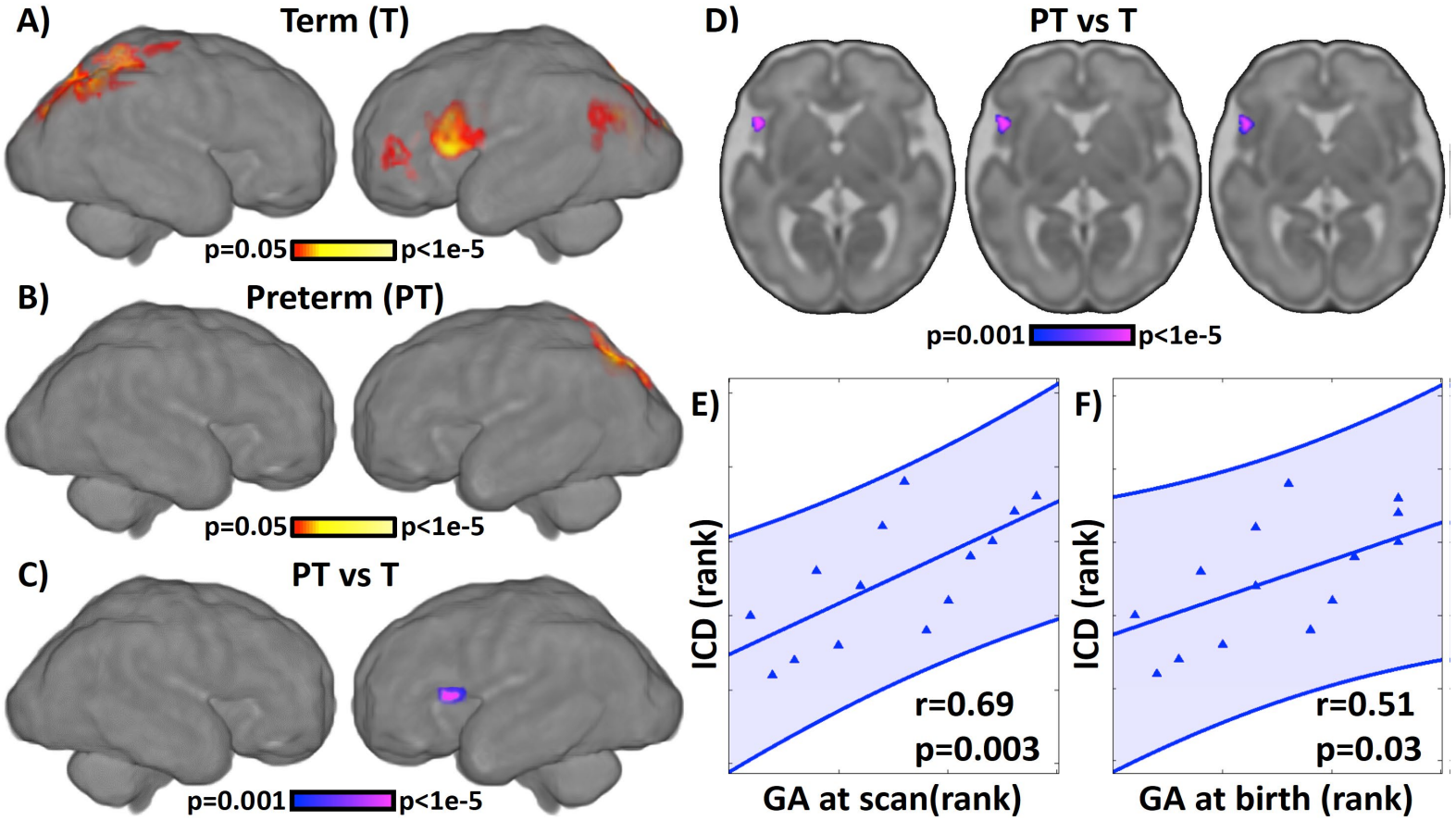


Are language systems altered prior to preterm birth?

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

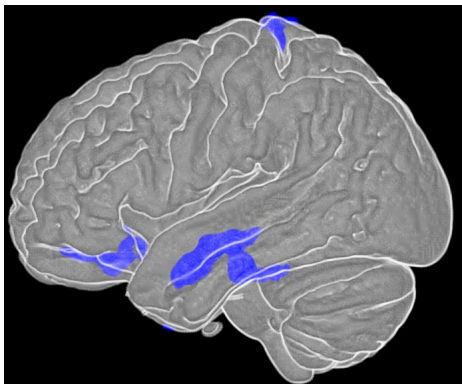
Alterations in language systems in the PT brain before birth



Conclusions

- Altered connectivity for language systems in developing preterm brain
  - Long-lasting and predictive

- Present during the late second and third trimesters of gestation in fetuses born preterm

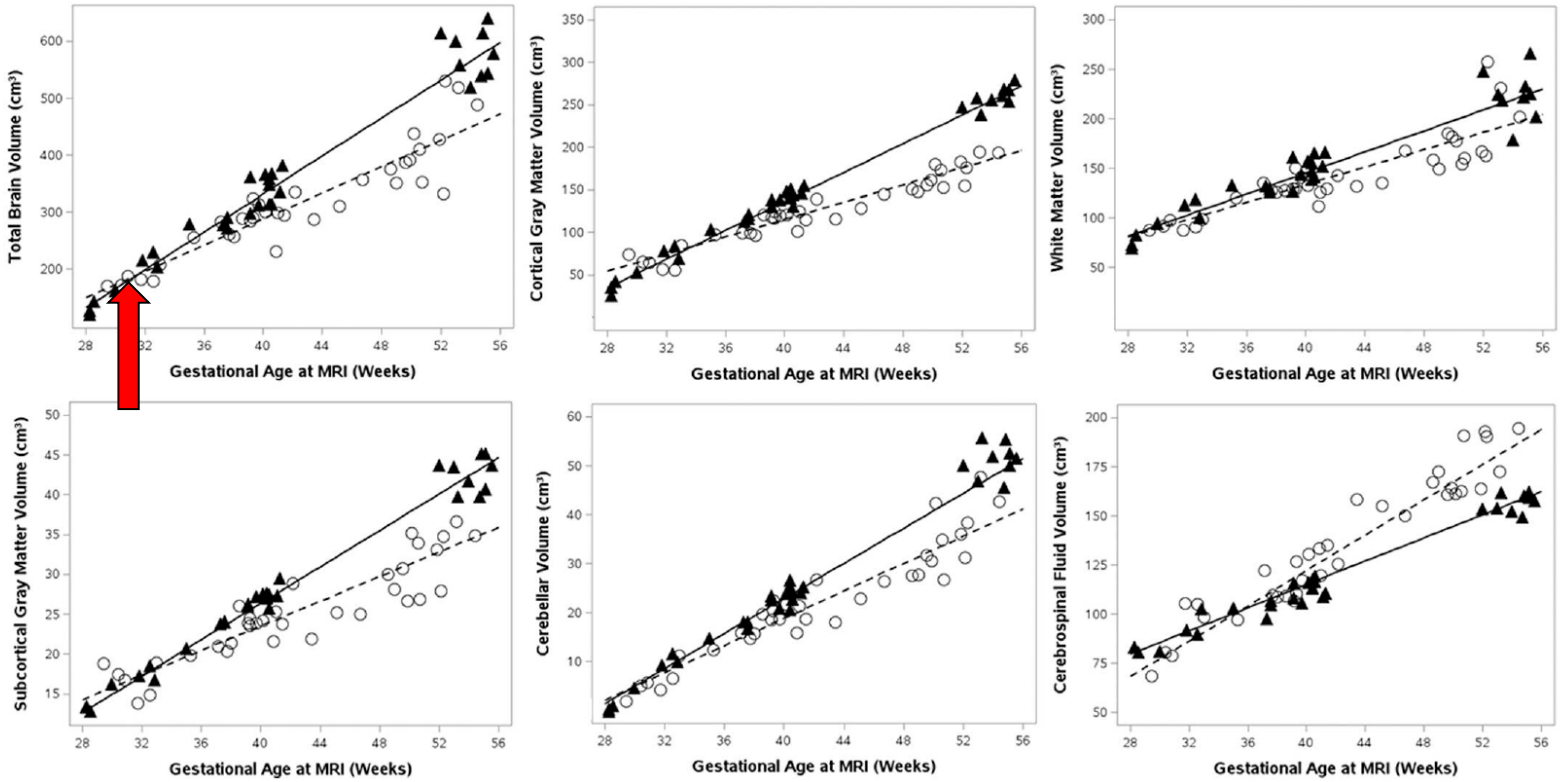


Congenital heart disease

- High risk for developmental disorders
  - 50% have language disorders
  - 23% with executive function difficulties
  - 10% are diagnosed with ASD

Impaired brain growth in CHD

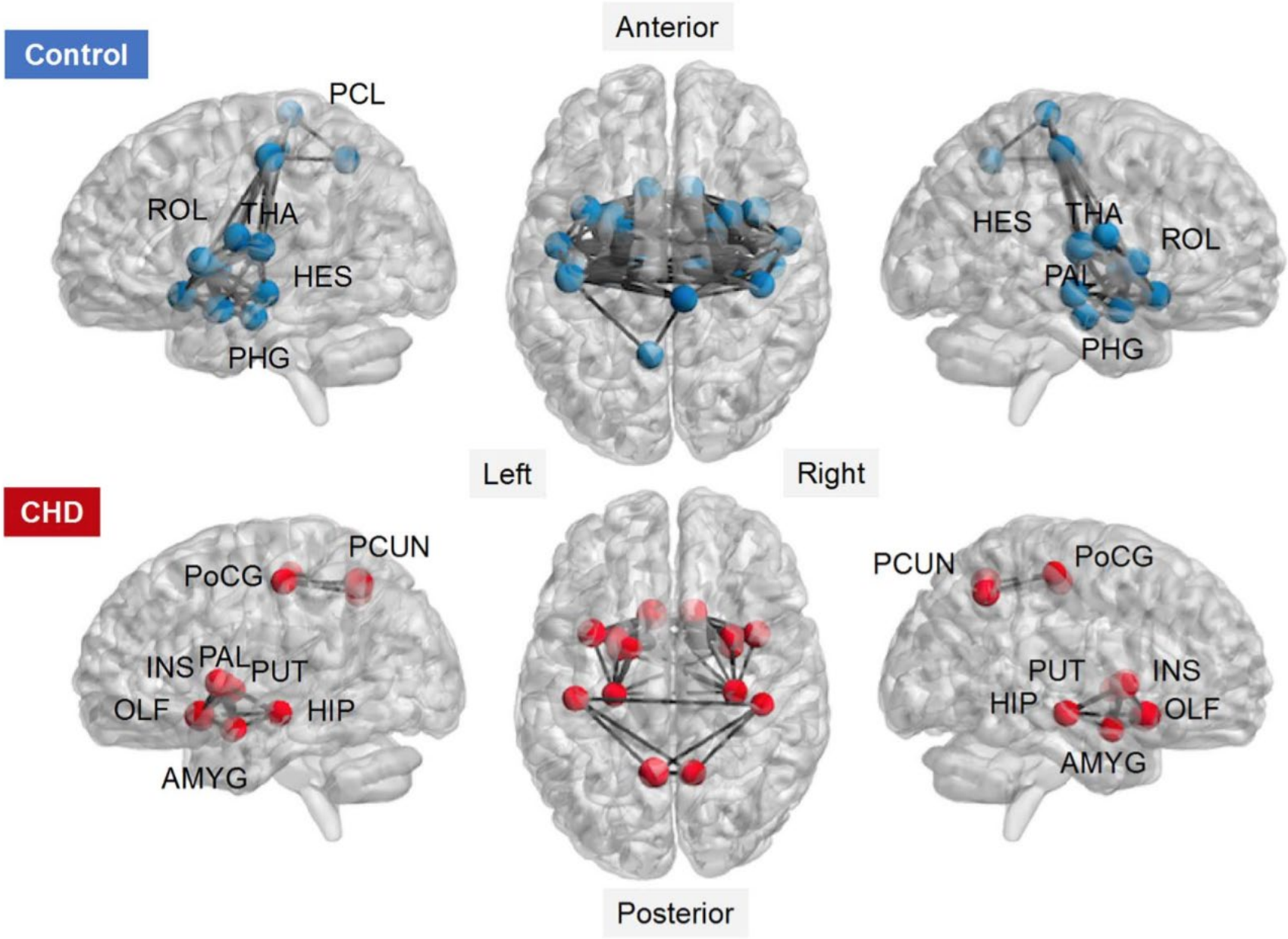
Ortinau et al, 2018



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 perisylvian language nodes are there; they aren't all connected.

Paradigm shift

- The NDD of CHD children had always been attributed to hypoxemia
  - Connectivity data do not support this hypothesis
- Emerging data suggested a subset of genes associated with both CHD and NDD
  - Jin et al, Nat Genet 2017, Contribution of rare inherited and de novo variants in 2871 CHD probands

CHD genes contribute to the connectome

Ji et al, 2018

- Hypothesis: Connectivity disorders in CHD subjects have a common genetic origin

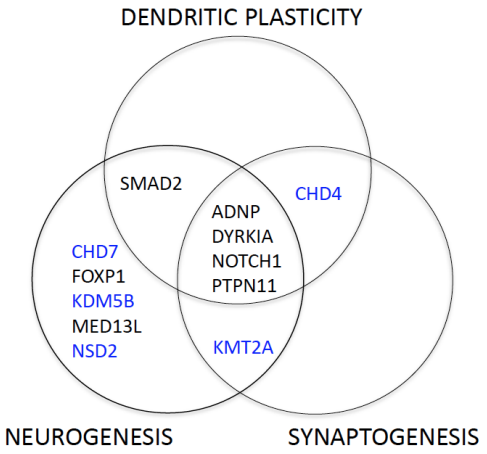
- Meta-analysis of genomic data
  - 3684 unique, published subjects with CHD; no trisomies
  - 1789 controls

- Previously published NDD genes (N=229) were individually annotated for connectome status
  - Neurogenesis, axonogenesis, growth cone, dendritogenesis, synaptogenesis, myelination, gliogenesis, connectome

12 NDD genes* with higher *de novo* mutation burden in the CHD population

- All contribute to the connectome (p=0.02)
  - 11/12 contribute to neurogenesis
  - 5/12 are chromatin modifiers (p=0.04)
- 5 genes reached genome wide significance (p≤2.5e-06)
  - PTPN11, CHD7, CHD4, KMT2A, NOTCH1, ADNP
- Top 2 genes
  - PTPN11 – p≤1.54e-34
  - CHD7 – p≤7.56e-2

* after Bonferroni correction



Genes in blue = chromatin modifiers

Unpublished data

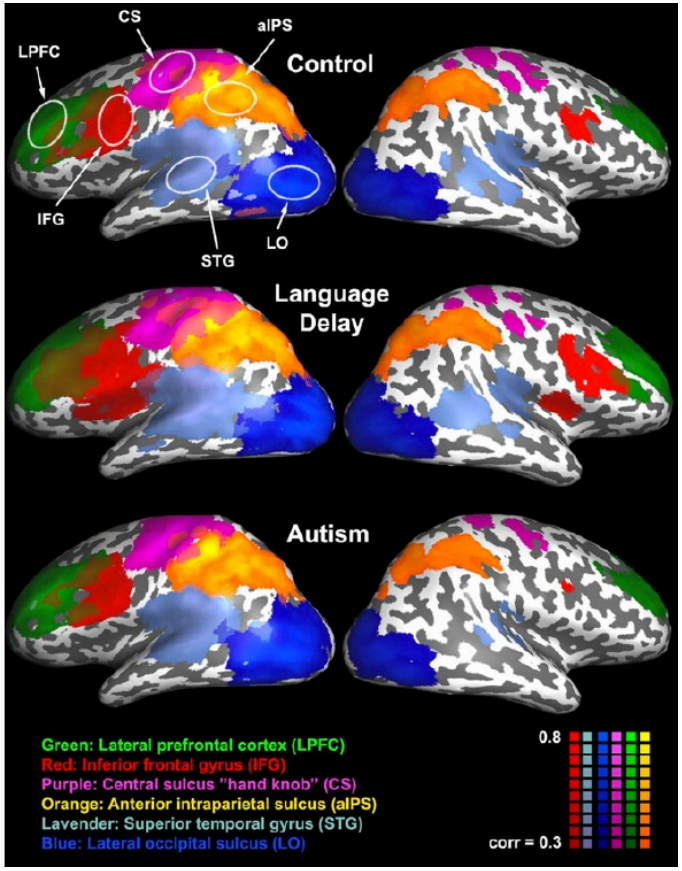
Conclusions

- Neurodevelopmental disorders in some CHD patients may be secondary to genes that alter both cardiac patterning and the connectome
- Fetal onset of the disorder

What about autism?

Disrupted neural connectivity in toddlers with autism

Dinstein et al, 2011

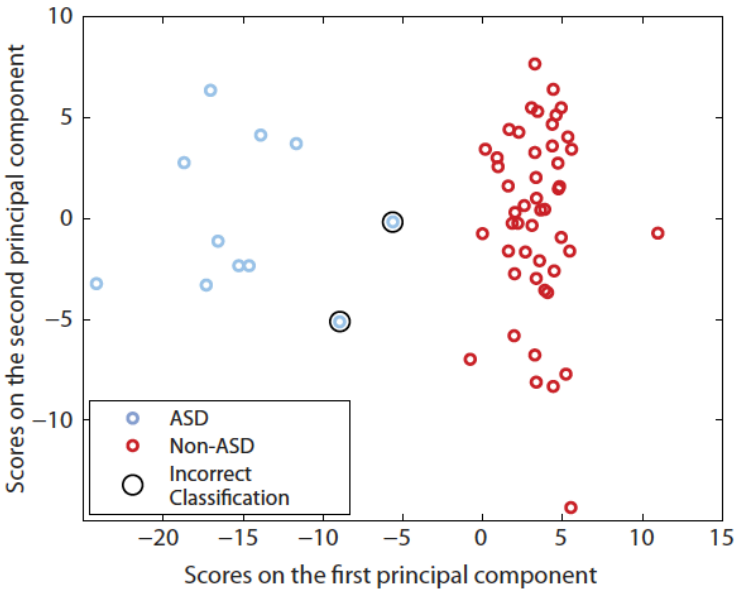


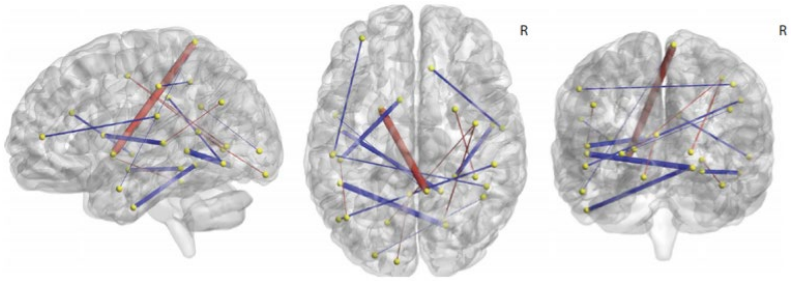
- Toddlers with ASD; controls
- RS-FC
- ASD had significantly weaker inter-hemispheric connectivity for language regions
  - Strength of connectivity correlated positively with language scores
  - Correlated negatively with autism severity

Functional neuroimaging of high risk 6 mo infants predicts autism at 24 months

Emerson et al, 2017

- 59 infants with high risk for ASD
- Rs-FC age 6 months
- Correctly predicted 9/11 with ASD at 24 months
  - PPV of 100% (95% CI 62.9 to 100)
- All 48 w/o ASD correctly classified
  - Neg PPV 96% (95% CI, 85.1 to 99.3)





Common themes: Work to be done

	PT birth	CHD	ASD
Language disorders	X	X	X
Alterations in lateralization	X	X	X
Prenatal onset	X	X	TBD
Correlation with outcome	X	X	TBD

Early, early diagnosis - early, early intervention

Many thanks!

- We thank the patients and their families.
- This work is supported by NIH R01HD081379, NIH UM1 HL098162, NIH R01 HL125885, NIH P50 HD093078 and NIH CTSA UL1 TR000142.