Early Assessment: Early Intervention
Imaging the developing brain

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Early Autism: Advances in Research and Clinical Practice

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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 heterogeneous in children with ASD
Lombardo et al, 2015

103 toddlers, ages 12-48 months, with serial language assessment
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 development 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

Better scores with left lateralized connectivity

r=0.65 p=0.002
What about neonates?
Preterms don’t laterallize for language

26 PT neonates < 28 wks GA, 25 controls, p < 0.001
Preterms don’t connect to homologue of L BA22

* $p < 0.001$
Preterms connect to homolog of motor cortex

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
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: prefer 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 microstructure 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
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 2\textsuperscript{nd} and 3\textsuperscript{rd} trimesters of gestation
  – Role of genetics and epigenetics

• Language is malleable
  – Role of very early intervention
Thanks!

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