Language, lateralization and the developing brain
Models for ASD

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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
R BA 40: Poorer scores with right lateralyzed 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

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

Lateralization is highly predictive of BSID III at 1 yr CA (p=0.007)
Fetuses lateralize at 30 weeks GA
ACE will tell us what this means

30-32 wks

34-36 wks

p=0.05

p<0.001
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
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

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Early, early diagnosis - early, early intervention
Many thanks!

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